EXHIBIT 5

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ALOXI safely and effectively. See full prescribing information for ALOXI

ALOXI® (palonosetron HCl) Injection for Intravenous Use
Initial U.S. Approval: 2003

----------RECENT MAJOR CHANGES----------

Indications and Usage,	
Postoperative Nausea and Vomiting (1.2)	02/2008
Dosage and Administration,	
Recommended Dosing (2.1)	02/2008
Warnings and Precautions,	
QTc Intervals (5.2) - Deletion	02/2008

----------INDICATIONS AND USAGE----------

ALOXI is a serotonin subtype 3 (5-HT_3) receptor antagonist indicated for:

- Moderately emetogenic cancer chemotherapy -- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses (1.1)
- Highly emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses (1.1)
- Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated (1.2)

----------DOSAGE AND ADMINISTRATION----------

Chemotherapy-Induced Nausea and Vomiting (2.1)

- Adult Dosage: a single 0.25 mg I.V. dose administered over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy.

Postoperative Nausea and Vomiting (2.1)

- Adult Dosage: a single 0.075 mg I.V. dose administered over 10 seconds immediately before the induction of anesthesia.

----------DOSAGE FORMS AND STRENGTHS----------

0.25 mg/5ml (free base) single-use vial (3)
0.075 mg/1.5ml (free base) single-use vial (3)

----------CONTRAINDICATIONS----------

ALOXI is contraindicated in patients known to have hypersensitivity to the drug or any of its components (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists (5.1)

----------ADVERSE REACTIONS----------

The most common adverse reactions in chemotherapy-induced nausea and vomiting (incidence ≥5%) are headache and constipation (6.1)

The most common adverse reactions in postoperative nausea and vomiting (incidence ≥ 2%) are QT prolongation, bradycardia, headache, and constipation.

To report SUSPECTED ADVERSE REACTIONS, contact MGI PHARMA at 1-800-562-5580 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

The potential for clinically significant drug interactions with palonosetron appears to be low (7)

---------- USE IN SPECIFIC POPULATIONS ----------

Safety and effectiveness in patients below the age of 18 years have not been established (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Patient Labeling

Revised: 02/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chemotherapy-Induced Nausea and Vomiting

ALOXI is indicated for:

- Moderately emetogenic cancer chemotherapy -- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
- Highly emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses

1.2 Postoperative Nausea and Vomiting

ALOXI is indicated for:

- the prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.

As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and vomiting must be avoided during the postoperative period, ALOXI is recommended even where the incidence of postoperative nausea and/or vomiting is low.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Chemotherapy-Induced Nausea and Vomiting

Dosage for Adults – a single 0.25 mg I.V. dose administered over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy.

Postoperative Nausea and Vomiting

Dosage for Adults - a single 0.075 mg I.V. dose administered over 10 seconds immediately before the induction of anesthesia.

2.2 Instructions for I.V. Administration

ALOXI is supplied ready for intravenous injection. ALOXI should not be mixed with other drugs. Flush the infusion line with normal saline before and after administration of ALOXI.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

3 DOSAGE FORM AND STRENGTHS

ALOXI is supplied as a single-use sterile, clear, colorless solution in glass vials that provide:

- 0.25 mg (free base) per 5 ml
- 0.075 mg (free base) per 1.5 ml.

4 CONTRAINDICATIONS

ALOXI is contraindicated in patients known to have hypersensitivity to the drug or any of its components. [*see Adverse Reactions (6.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other 5-HT_3 receptor antagonists.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Chemotherapy-Induced Nausea and Vomiting

In clinical trials for the prevention of nausea and vomiting induced by moderately or highly emetogenic chemotherapy, 1374 adult patients received palonosetron. Adverse reactions were similar in frequency and severity with ALOXI and ondansetron or dolasetron. Following is a listing of all adverse reactions reported by ≥ 2% of patients in these trials (Table 1).

Table 1: Adverse Reactions from Chemotherapy-Induced Nausea and Vomiting Studies ≥ 2% in any Treatment Group

Event	Aloxi 0.25 mg (N=633)	Ondansetron 32 mg I.V. (N=410)	Dolasetron 100 mg I.V. (N=194)
Headache	60 (9%)	34 (8%)	32 (16%)
Constipation	29 (5%)	8 (2%)	12 (6%)
Diarrhea	8 (1%)	7 (2%)	4 (2%)
Dizziness	8 (1%)	9 (2%)	4 (2%)
Fatigue	3 (< 1%)	4 (1%)	4 (2%)
Abdominal Pain	1 (< 1%)	2 (< 1%)	3 (2%)
Insomnia	1 (< 1%)	3 (1%)	3 (2%)

In other studies, 2 subjects experienced severe constipation following a single palonosetron dose of approximately 0.75 mg, three times the recommended dose. One patient received a 10 mcg/kg oral dose in a post-operative nausea and vomiting study and one healthy subject received a 0.75 mg I.V. dose in a pharmacokinetic study.

In clinical trials, the following infrequently reported adverse reactions, assessed by investigators as treatment-related or causality unknown, occurred following administration of ALOXI to adult patients receiving concomitant cancer chemotherapy:

Cardiovascular**:** 1%: non-sustained tachycardia, bradycardia, hypotension, < 1%: hypertension, myocardial ischemia, extrasystoles, sinus tachycardia, sinus arrhythmia, supraventricular extrasystoles and QT prolongation. In many cases, the relationship to ALOXI was unclear.

Dermatological: < 1%: allergic dermatitis, rash.

Hearing and Vision: < 1%: motion sickness, tinnitus, eye irritation and amblyopia.

Gastrointestinal System: 1%: diarrhea, < 1%: dyspepsia, abdominal pain, dry mouth, hiccups and flatulence.

General: 1%: weakness, < 1%: fatigue, fever, hot flash, flu-like syndrome.

Liver: < 1%: transient, asymptomatic increases in AST and/or ALT and bilirubin. These changes occurred predominantly in patients receiving highly emetogenic chemotherapy.

Metabolic: 1%: hyperkalemia, < 1%: electrolyte fluctuations, hyperglycemia, metabolic acidosis, glycosuria, appetite decrease, anorexia.

Musculoskeletal: < 1%: arthralgia.

Nervous System: 1%: dizziness, < 1%: somnolence, insomnia, hypersomnia, paresthesia.

Psychiatric: 1%: anxiety, < 1%: euphoric mood.

Urinary System: < 1%: urinary retention.

Vascular: < 1%: vein discoloration, vein distention.

6.2 Postoperative Nausea and Vomiting

The adverse reactions cited in Table 2 were reported in ≥ 2% of adults receiving I.V. Aloxi 0.075 mg immediately before induction of anesthesia in one phase 2 and two phase 3 randomized placebo-controlled trials. Rates of events between palonosetron and placebo groups were indistinguishable. Some events are known to be associated with, or may be exacerbated by concomitant perioperative and intraoperative medications administered in this surgical population. Please refer to Section 12.2, thorough QT/QTc study results, for definitive data demonstrating the lack of palonosetron effect on QT/QTc.

Table 2: Adverse Reactions from Postoperative Nausea and Vomiting Studies ≥ 2% in any Treatment Group

Event	Aloxi 0.075 mg (N=336)	Placebo (N=369)
Electrocardiogram QT prolongation	16 (5%)	11 (3%)
Bradycardia	13 (4%)	16 (4%)
Headache	11 (3%)	14 (4%)
Constipation	8 (2%)	11(3%)

In these clinical trials, the following infrequently reported adverse reactions, assessed by investigators as treatment-related or causality unknown, occurred following administration of ALOXI to adult patients receiving concomitant perioperative and intraoperative medications including those associated with anesthesia:

Cardiovascular**:** 1% Electrocardiogram QTc prolongation, sinus bradycardia, tachycardia; < 1%: blood pressure decreased, hypotension, hypertension, arrhythmia, ventricular extrasystoles, generalized edema; ECG T wave amplitude decreased, platelet count decreased. The frequency of these adverse effects did not appear to be different from placebo.

Dermatological: 1%: pruritus.

Gastrointestinal System: 1%: flatulence, < 1%: Dry mouth, upper abdominal pain, salivary hypersecretion, dyspepsia, diarrhea, intestinal hypomotility, anorexia.

General: < 1%: chills.

Liver: 1%: increases in AST and/or ALT< 1%: hepatic enzyme increased

Metabolic: < 1%: hypokalemia, anorexia.

Nervous System: < 1%: dizziness.

Respiratory: < 1%: hypoventilation, laryngospasm.

Urinary System: 1%: urinary retention.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ALOXI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Very rare cases (<1/10,000) of hypersensitivity reactions and injection site reactions (burning, induration, discomfort and pain) were reported from postmarketing experience of ALOXI 0.25 mg in the prevention of chemotherapy-induced nausea and vomiting.

7 DRUG INTERACTIONS

Palonosetron is eliminated from the body through both renal excretion and metabolic pathways with the latter mediated via multiple CYP enzymes. Further *in vitro* studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 (CYP2C19 was not investigated) nor does it induce the activity of CYP1A2, CYP2D6, or CYP3A4/5. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low.

Coadministration of 0.25 mg I.V. palonosetron and 20 mg I.V. dexamethasone in healthy subjects revealed no pharmacokinetic drug-interactions between palonosetron and dexamethasone.

In an interaction study in healthy subjects where palonosetron 0.25 mg (I.V. bolus) was administered on day 1 and oral aprepitant for 3 days (125 mg/80 mg/80mg), the pharmacokinetics of palonosetron were not significantly altered (AUC: no change, Cmax: 15% increase).

A study in healthy volunteers involving single-dose I.V. palonosetron (0.75 mg) and steady state oral metoclopramide (10 mg four times daily) demonstrated no significant pharmacokinetic interaction.

In controlled clinical trials, ALOXI injection has been safely administered with corticosteroids, analgesics, antiemetics/antinauseants, antispasmodics and anticholinergic agents.

Palonosetron did not inhibit the antitumor activity of the five chemotherapeutic agents tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C) in murine tumor models.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Category B

Teratology studies have been performed in rats at oral doses up to 60 mg/kg/day (1894 times the recommended human intravenous dose based on body surface area) and rabbits at oral doses up to 60 mg/kg/day (3789 times the recommended human intravenous dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to palonosetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, palonosetron should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

Palonosetron has not been administered to patients undergoing labor and delivery, so its effects on the mother or child are unknown.

8.3 Nursing Mothers

It is not known whether palonosetron is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and the potential for tumorigenicity shown for palonosetron in the rat carcinogenicity study, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in patients below the age of 18 years have not been established.

8.5 Geriatric Use

Population pharmacokinetics analysis did not reveal any differences in palonosetron pharmacokinetics between cancer patients ≥ 65 years of age and younger patients (18 to 64 years). Of the 1374 adult cancer patients in clinical studies of palonosetron, 316 (23%) were ≥ 65 years old, while 71 (5%) were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these subjects and the younger subjects, but greater sensitivity in some older individuals cannot be ruled out. No dose adjustment or special monitoring are required for geriatric patients.

Of the 1520 adult patients in Aloxi PONV clinical studies, 73 (5%) were ≥65 years old. No overall differences in safety were observed between older and younger subjects in these studies, though the possibility of heightened sensitivity in some older individuals cannot be excluded. No differences in efficacy were observed in geriatric patients for the CINV indication and none are expected for geriatric PONV patients. However, Aloxi efficacy in geriatric patients has not been adequately evaluated.

8.6 Renal Impairment

Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure increased by approximately 28% in severe renal impairment relative to healthy subjects. Dosage adjustment is not necessary in patients with any degree of renal impairment.

8.7 Hepatic Impairment

Hepatic impairment does not significantly affect total body clearance of palonosetron compared to the healthy subjects. Dosage adjustment is not necessary in patients with any degree of hepatic impairment.

8.8 Race

Intravenous palonosetron pharmacokinetics was characterized in twenty-four healthy Japanese subjects over the dose range of 3 – 90 mcg/kg.

Total body clearance was 25% higher in Japanese subjects compared to Whites, however, no dose adjustment is required. The pharmacokinetics of palonosetron in Blacks has not been adequately characterized.

10 OVERDOSAGE

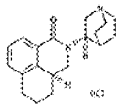
There is no known antidote to ALOXI. Overdose should be managed with supportive care.

Fifty adult cancer patients were administered palonosetron at a dose of 90 mcg/kg (equivalent to 6 mg fixed dose) as part of a dose ranging study. This is approximately 25 times the recommended dose of 0.25 mg. This dose group had a similar incidence of adverse events compared to the other dose groups and no dose response effects were observed.

Dialysis studies have not been performed, however, due to the large volume of distribution, dialysis is unlikely to be an effective treatment for palonosetron overdose. A single intravenous dose of palonosetron at 30 mg/kg (947 and 474 times the human dose for rats and mice, respectively, based on body surface area) was lethal to rats and mice. The major signs of toxicity were convulsions, gasping, pallor, cyanosis and collapse.

11 DESCRIPTION

ALOXI (palonosetron hydrochloride) is an antiemetic and antinauseant agent. It is a serotonin subtype 3 (5-HT_3) receptor antagonist with a strong binding affinity for this receptor. Chemically, palonosetron hydrochloride is: (3a<u>S</u>)-2-[(<u>S</u>)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline hydrochloride. The empirical formula is $C_{19}H_{24}N_2O.HCl$, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer and has the following structural formula:



Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

ALOXI injection is a sterile, clear, colorless, non pyrogenic, isotonic, buffered solution for intravenous administration. ALOXI injection is available as 5 mL single use vial or 1.5 mL single use vial. Each 5 mL vial contains 0.25 mg palonosetron base as hydrochloride, 207.5 mg mannitol, disodium edetate and citrate buffer in water for intravenous administration.

Each 1.5 mL vial contains 0.075 mg palonosetron base as hydrochloride, 83 mg mannitol, disodium edetate and citrate buffer in water for intravenous administration.

The pH of the solution in the 5 mL and 1.5 mL vials is 4.5 to 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors.

Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex.

Postoperative nausea and vomiting is influenced by multiple patient, surgical and anesthesia related factors and is triggered by release of 5-HT in a cascade of neuronal events involving both the central nervous system and the gastrointestinal tract. The 5-HT_3 receptor has been demonstrated to selectively participate in the emetic response.

12.2 Pharmacodynamics

The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in CINV clinical trials. In PONV clinical trials the effect of palonosetron on the QTc interval was no different from placebo. In non-clinical studies palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarization and to prolong action potential duration.

The effect of palonosetron on QTc interval was evaluated in a double blind, randomized, parallel, placebo and positive (moxifloxacin) controlled trial in adult men and women. The objective was to evaluate the ECG effects of I.V. administered palonosetron at single doses of 0.25, 0.75 or 2.25 mg in 221 healthy subjects. The study demonstrated no significant effect on any ECG interval including QTc duration (cardiac repolarization) at doses up to 2.25 mg.

12.3 Pharmacokinetics

After intravenous dosing of palonosetron in healthy subjects and cancer patients, an initial decline in plasma concentrations is followed by a slow elimination from the body. Mean maximum plasma concentration (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) are generally dose-proportional over the dose range of 0.3–90 mcg/kg in healthy subjects and in cancer patients. Following single I.V. dose of palonosetron at 3 mcg/kg (or 0.21 mg/70 kg) to six cancer patients, mean (±SD) maximum plasma concentration was estimated to be 5.6 ± 5.5 ng/mL and mean AUC was 35.8 ± 20.9 ng•hr/mL.

Following I.V. administration of palonosetron 0.25 mg once every other day for 3 doses in 11 cancer patients, the mean increase in plasma palonosetron concentration from Day 1 to Day 5 was 42±34%. Following I.V. administration of palonosetron 0.25 mg once daily for 3 days in 12 healthy subjects, the mean (±SD) increase in plasma palonosetron concentration from Day 1 to Day 3 was 110±45%.

After intravenous dosing of palonosetron in patients undergoing surgery (abdominal surgery or vaginal hysterectomy), the pharmacokinetic characteristics of palonosetron were similar to those observed in cancer patients.

<u>Distribution</u>

Palonosetron has a volume of distribution of approximately 8.3 ± 2.5 L/kg. Approximately 62% of palonosetron is bound to plasma proteins.

<u>Metabolism</u>

Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT_3 receptor antagonist activity of palonosetron. *In vitro* metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

<u>Elimination</u>

After a single intravenous dose of 10 mcg/kg [^{14}C]-palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine with palonosetron representing approximately 40% of the administered dose. In healthy subjects, the total body clearance of palonosetron was 160 ± 35 mL/h/kg and renal clearance was 66.5± 18.2 mL/h/kg. Mean terminal elimination half-life is approximately 40 hours.

Special Populations

[*See USE IN SPECIFIC POPULATIONS (8.5 – 8.8)*

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in CD-1 mice, animals were treated with oral doses of palonosetron at 10, 30 and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic. The highest tested dose produced a systemic exposure to palonosetron (Plasma AUC) of about 150 to 289 times the human exposure (AUC= 29.8 ng•h/mL) at the recommended intravenous dose of 0.25 mg. In a 104-week carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30 and 60 mg/kg/day and 15, 45 and 90 mg/kg/day, respectively. The highest doses produced a systemic exposure to palonosetron (Plasma AUC) of 137 and 308 times the human exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant

pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the *ex vivo* hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronucleus test. It was, however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test.

Palonosetron at oral doses up to 60 mg/kg/day (about 1894 times the recommended human intravenous dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

14.1 Chemotherapy Induced Nausea and Vomiting

Efficacy of single-dose palonosetron injection in preventing acute and delayed nausea and vomiting induced by both moderately and highly emetogenic chemotherapy was studied in three Phase 3 trials and one Phase 2 trial. In these double-blind studies, complete response rates (no emetic episodes and no rescue medication) and other efficacy parameters were assessed through at least 120 hours after administration of chemotherapy. The safety and efficacy of palonosetron in repeated courses of chemotherapy was also assessed.

Moderately Emetogenic Chemotherapy

Two Phase 3, double-blind trials involving 1132 patients compared single-dose I.V. ALOXI with either single-dose I.V. ondansetron (study 1) or dolasetron (study 2) given 30 minutes prior to moderately emetogenic chemotherapy including carboplatin, cisplatin ≤ 50 mg/m², cyclophosphamide < 1500 mg/m², doxorubicin > 25 mg/m², epirubicin, irinotecan, and methotrexate > 250 mg/m². Concomitant corticosteroids were not administered prophylactically in study 1 and were only used by 4-6% of patients in study 2. The majority of patients in these studies were women (77%), White (65%) and naïve to previous chemotherapy (54%). The mean age was 55 years.

Highly Emetogenic Chemotherapy

A Phase 2, double-blind, dose-ranging study evaluated the efficacy of single-dose I.V. palonosetron from 0.3 to 90 mcg/kg (equivalent to < 0.1 mg to 6 mg fixed dose) in 161 chemotherapy-naïve adult cancer patients receiving highly-emetogenic chemotherapy (either cisplatin ≥ 70 mg/m² or cyclophosphamide > 1100 mg/m²). Concomitant corticosteroids were not administered prophylactically. Analysis of data from this trial indicates that 0.25 mg is the lowest effective dose in preventing acute nausea and vomiting induced by highly emetogenic chemotherapy.

A Phase 3, double-blind trial involving 667 patients compared single-dose I.V. ALOXI with single-dose I.V. ondansetron (study 3) given 30 minutes prior to highly emetogenic chemotherapy including cisplatin ≥ 60 mg/m², cyclophosphamide > 1500 mg/m², and dacarbazine. Corticosteroids were co-administered prophylactically before chemotherapy in 67% of patients. Of the 667 patients, 51% were women, 60% White, and 59% naïve to previous chemotherapy. The mean age was 52 years.

Efficacy Results

The antiemetic activity of ALOXI was evaluated during the acute phase (0-24 hours) [Table 3], delayed phase (24-120 hours) [Table 4], and overall phase (0-120 hours) [Table 5] post-chemotherapy in Phase 3 trials.

Table 3: Prevention of Acute Nausea and Vomiting (0-24 hours): Complete Response Rates

Chemotherapy	Study	Treatment Group	N [a]	% with Complete Response	p-value [b]	97.5% Confidence Interval ALOXI minus Comparator [c]
Moderately Emetogenic	1	ALOXI 0.25 mg	189	81	0.009	[2%, 23%]
		Ondansetron 32 mg I.V.	185	69		
	2	ALOXI 0.25 mg	189	63	NS	[-2%, 22%]
		Dolasetron 100 mg I.V.	191	53		
Highly Emetogenic	3	ALOXI 0.25 mg	223	59	NS	[-9%, 13%]
		Ondansetron 32 mg I.V.	221	57		

-10 -5 0 5 10 15 20 25 30 35
Difference in Complete Response Rates

a Intent-to-treat cohort
b 2-sided Fisher's exact test. Significance level at α=0.025.
c These studies were designed to show non-inferiority. A lower bound greater than –15% demonstrates non-inferiority between ALOXI and comparator.

These studies show that ALOXI was effective in the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy. In study 3, efficacy was greater when prophylactic corticosteroids were administered concomitantly. Clinical superiority over other 5-HT3 receptor antagonists has not been adequately demonstrated in the acute phase.

Table 4: Prevention of Delayed Nausea and Vomiting (24-120 hours): Complete Response Rates

Chemotherapy	Study	Treatment Group	N [a]	% with Complete Response	p-value [b]	97.5% Confidence Interval ALOXI minus Comparator [c]
Moderately Emetogenic	1	ALOXI 0.25 mg	189	74	<0.001	[8%, 30%]
		Ondansetron 32 mg I.V.	185	55		
	2	ALOXI 0.25 mg	189	54	0.004	[3%, 27%]
		Dolasetron 100 mg I.V.	191	39		

-10 -5 0 5 10 15 20 25 30 35
Difference in Complete Response Rates

a Intent-to-treat cohort
b 2-sided Fisher's exact test. Significance level at α=0.025.
c These studies were designed to show non-inferiority. A lower bound greater than –15% demonstrates non-inferiority between ALOXI and comparator.

These studies show that ALOXI was effective in the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.

Table 5: Prevention of Overall Nausea and Vomiting (0-120 hours): Complete Response Rates

Chemotherapy	Study	Treatment Group	N[a]	% with Complete Response	p-value[b]	97.5% Confidence Interval ALOXI minus Comparator[c]
Moderately Emetogenic	1	ALOXI 0.25 mg	189	69	<0.001	[7%, 31%]
		Ondansetron 32 mg I.V.	185	50		
	2	ALOXI 0.25 mg	189	46	0.021	[0%, 24%]
		Dolasetron 100 mg I.V.	191	34		-10 -5 0 5 10 15 20 25 30 35 Difference in Complete Response Rates

a Intent-to-treat cohort
b 2-sided Fisher's exact test. Significance level at α=0.025.
c These studies were designed to show non-inferiority. A lower bound greater than –15% demonstrates non-inferiority between ALOXI and comparator.

These studies show that ALOXI was effective in the prevention of nausea and vomiting throughout the 120 hours (5 days) following initial and repeat courses of moderately emetogenic cancer chemotherapy.

14.2 Postoperative Nausea and Vomiting

In one multicenter, randomized, stratified, double-blind, parallel-group, phase 3 clinical study (Study 1), palonosetron was compared with placebo for the prevention of PONV in 546 patients undergoing abdominal and gynecological surgery. All patients received general anesthesia. Study 1 was a pivotal study conducted predominantly in the US in the out-patient setting for patients undergoing elective gynecologic or abdominal laparoscopic surgery and stratified at randomization for the following risk factors: gender, non-smoking status, history of post operative nausea and vomiting and/or motion sickness.

In Study 1 patients were randomized to receive palonosetron 0.025 mg, 0.050 mg or 0.075 mg or placebo, each given intravenously immediately prior to induction of anesthesia. The antiemetic activity of palonosetron was evaluated during the 0 to 72 hour time period after surgery.

Of the 138 patients treated with 0.075 mg palonosetron in Study 1 and evaluated for efficacy, 96% were women; 66% had a history of PONV or motion sickness; 85% were non-smokers. As for race, 63% were White, 20% were Black, 15% were Hispanic, and 1% were Asian. The age of patients ranged from 21 to 74 years, with a mean age of 37.9 years. Three patients were greater than 65 years of age.

Co-primary efficacy measures were Complete Response (CR) defined as no emetic episode and no use of rescue medication in the 0-24 and in the 24-72 hours postoperatively.

Secondary efficacy endpoints included:

- Complete Response (CR) 0-48 and 0-72 hours
- Complete Control (CC) defined as CR and no more than mild nausea
- Severity of nausea (none, mild, moderate, severe)

The primary hypothesis in Study 1 was that at least one of the three palonosetron doses were superior to placebo.

Results for Complete Response in Study 1 for 0.075 mg palonosetron versus placebo are described in the following table.

Table 6: Prevention of Postoperative Nausea and Vomiting: Complete Response (CR), Study 1, Palonosetron 0.075 mg Vs Placebo

Treatment	n/N (%)	Palonosetron Vs Placebo	
		Δ	p-value*
Co-primary Endpoints			
CR 0-24 hours			
Palonosetron	59/138 (42.8%)	16.8%	0.004
Placebo	35/135 (25.9%)		
CR 24-72 hours			
Palonosetron	67/138 (48.6%)	7.8%	0.188
Placebo	55/135 (40.7%)		

* To reach statistical significance for each co-primary endpoint, the required significance limit for the lowest p-value was p<0.017.
Δ Difference (%): palonosetron 0.075 mg minus placebo

Palonosetron 0.075 mg reduced the severity of nausea compared to placebo. Analyses of other secondary endpoints indicate that palonosetron 0.075 mg was numerically better than placebo, however, statistical significance was not formally demonstrated.

A phase 2 randomized, double-blind, multicenter, placebo-controlled, dose ranging study was performed to evaluate I.V. palonosetron for the prevention of post-operative nausea and vomiting following abdominal or vaginal hysterectomy. Five I.V. palonosetron doses (0.1, 0.3, 1.0, 3.0 and 30 µg/kg) were evaluated in a total of 381 intent-to-treat patients. The primary efficacy measure was the proportion of patients with CR in the first 24 hours after recovery from surgery. The lowest effective dose was palonosetron 1 µg/kg (approximately 0.075 mg) which had a CR rate of 44% versus 19% for placebo, p=0.004. Palonosetron 1 µg/kg also significantly reduced the severity of nausea versus placebo, p=0.009.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC # 58063-797-25, 0.25 mg/5 mL (free base) single-use vial individually packaged in a carton.

NDC # 58063-797-37, 0.075 mg/1.5 mL (free base) single-use vial packaged in a carton containing 5 vials.

Storage

- Store at controlled temperature of 20–25°C (68°F–77°F). Excursions permitted to 15–30 °C (59-86°F).
- Protect from freezing.
- Protect from light.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.2)

17.1 Instructions for Patients

Patients should be advised to report to their physician all of their medical conditions, any pain, redness, or swelling in and around the infusion site *[see Adverse Reactions 6.2]*.

Patients should be instructed to read the patient insert.

17.2 FDA-Approved Patient Labeling

Patient Information

ALOXI® (Ah-lock-see)
Palonosetron HCl injection

Read the Patient Information that comes with ALOXI before your treatment with ALOXI and each time you get ALOXI. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have questions about ALOXI, ask your doctor or pharmacist.

What is ALOXI?

ALOXI is a medicine called an "antiemetic." ALOXI is used in adults to help prevent the nausea and vomiting that happens:

- right away with certain anti-cancer medicines (chemotherapy)
- or later with certain anti-cancer medicines
- right away or later after recovery from anesthesia after surgery

What is ALOXI used for?

ALOXI is used to prevent nausea and vomiting that may happen:

- soon after taking certain anti-cancer medicines
- later after taking certain anti-cancer medicines
- soon after recovery from anesthesia after surgery

Who should not take ALOXI?

Do not take ALOXI if you are allergic to any of the ingredients in ALOXI. The active ingredient is palonosetron hydrochloride. See the end of this leaflet for a complete list of ingredients in ALOXI.

ALOXI has not been studied in children under 18 years of age.

What should I tell my doctor before using ALOXI?

Tell your doctor about all of your medical conditions, including if you:

- **are pregnant.** It is not known if ALOXI may harm your unborn baby. You and your doctor should decide if ALOXI is right for you.
- **are breastfeeding.** It is not known if ALOXI passes into your milk and if it can harm your baby. You should choose to either take ALOXI or breastfeed, but not both.

Tell your doctor about all of the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements.

How should I use ALOXI?

ALOXI is given in your vein by I.V. (intravenous) injection. It is only given to you by a healthcare provider in a hospital or clinic. ALOXI is usually injected into your vein about 30 minutes before you get your anti-cancer medicine (chemotherapy) or immediately before anesthesia for surgery

What are the possible side effects of ALOXI?

The most common side effects of ALOXI are headache and constipation. Diarrhea and dizziness have also been observed.

These are not all the side effects from ALOXI. For more information ask your doctor or pharmacist.

General information about ALOXI

Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. ALOXI was prescribed for your medical condition.

This leaflet summarizes the most important information about ALOXI. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ALOXI that is written for health professionals. You can also visit the ALOXI web site at www.ALOXI.com.

What are the ingredients in ALOXI?

Active ingredient: palonosetron hydrochloride
Inactive ingredients: mannitol, disodium edetate, and citrate buffer in water

Rx Only

Mfd by Catalent Pharma Solutions, Albuquerque, NM, USA or Pierre Fabre, Médicament Production, Idron, Aquitaine, France and Helsinn Birex Pharmaceuticals, Dublin, Ireland

HELSINN, Mfd for Helsinn Healthcare SA, Switzerland

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EXHIBIT 6

Drugs 25 (Suppl. 1): 1-7 (1983)
0012-6667/83/0002-0001/$03.50/0

Nausea and Vomiting as Major Complications of Cancer Chemotherapy

John Laszlo

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Summary

Significant advances in the treatment of certain disseminated malignancies have been accompanied by an increased awareness of the consequences of inadequate antiemetic therapy. Nausea and vomiting are predisposing factors to patient non-compliance with treatment regimens and impose mental and physical suffering that diminishes the quality of life. The extent of medical complications associated with vomiting depends on its severity and duration and can include oesophageal tears, bone fractures, malnutrition and major metabolic derangements.

The pharmacological management of chemotherapy-induced nausea and vomiting is influenced by the aetiology and mechanism as well as whether therapy is to take place in the hospital or outpatient setting. No single drug is successful in all cases. Side effects due to antiemetic drugs also limit their usefulness.

Major treatment alternatives at present include the phenothiazines, antihistamines, benzquinamide derivatives, butyrophenones such as haloperidol, the dopamine receptor antagonist domperidone, and metoclopramide. Cannabinoids, particularly Δ-9-tetrahydrocannabinol and nabilone have stimulated considerable research interest. Studies of the role of high dose corticosteroids either alone or in combination with other antiemetics have also been undertaken.

Newer chemotherapeutic regimens are more emetic than in the past. Inadequate management of nausea and vomiting is deleterious to the health and well-being of patients and any delay in providing an aggressive therapeutic approach aggravates the problem. This symposium is designed to provide some answers to this therapeutic problem.

Just over 2 decades ago, the goal of curing patients of disseminated malignancy was realised when single agent chemotherapy for choriocarcinoma in women was found to be successful. Since that time, a massive international cancer research effort has resulted in more aggressive and innovative programmes for all types of oncology patients. Now the possibility of cure exists for patients with testicular cancer, diffuse histiocytic lymphoma, acute lymphocytic leukaemia, and a number of childhood cancers. Furthermore, the use of multi-agent chemotherapy as an adjuvant to sur-

gical removal of primary tumours is clearly beneficial in diseases such as breast cancer. Unfortunately, even aggressive use of multi-agent chemotherapy or additive radiation therapy has not yet cured common disseminated malignancies originating from the breast, the gastrointestinal tract or the lung, although remissions have been achieved with variable frequency and length.

Successful treatment depends upon the ability of physicians to develop strategies for preventing or managing the potential consequences of bone marrow suppression and life-threatening thrombocytopenia and granulocytopenia, as well as preventing serious toxicity to vital organs. Major advances in transfusing platelets, in recognising and treating opportunistic infections, and in preventing unique organ toxicities from drugs such as cisplatin, bleomycin and doxorubicin, have enabled major advances in the treatment of cancer.

Until the mid-1970s, very little clinical antiemetic research had been carried out. Possible reasons for this are that nausea and vomiting had not previously been considered complications of cancer chemotherapy, the number of emetogenic chemotherapy programmes had markedly increased, and supportive care had generally not had as much research appeal as anticancer therapy. In a recent review, Penta et al. (1982) reported that of 57 antiemetic studies in cancer patients between 1960 and 1981, 47 were carried out between 1978 and 1981.

1. Consequences of Inadequate Antiemetic Therapy

1.1 Patient Non-compliance

There are 3 major consequences of inadequate antiemetic therapy. The most obvious concern is the problem of compliance with treatment. High dose cisplatin administration causes serious nausea and vomiting in almost 100% of patients, and the more widely used cyclophosphamide-methotrexate-5-fluorouracil (CMF) programme yields a 75% incidence of nausea and/or vomiting. It is difficult to estimate the number of patients who drop out of lengthy therapy programmes, decline to participate in such programmes as CMF adjuvant chemotherapy, or have therapy postponed beyond the desirable limits. However, inadequate compliance because of severe nausea and vomiting may be as high as 25 to 50%. In some instances, patients have actually declined potentially curative therapy (Laszlo, 1982). In cases such as curable lymphoma or testicular cancer, it is important that patients do not refuse appropriate therapy.

1.2 Patient Discomfort

The second major concern is attending to the comfort of patients and recognising the mental and physical suffering which affects their jobs and personal lives. Women receiving monthly adjuvant chemotherapy for breast cancer are often debilitated by nausea and vomiting for 3 or 4 days and unable to work during that time but they want and need to maintain their jobs. The issue here is not one of compliance but rather of attention to the quality of life. Adequate antiemetic therapy is also needed to prevent 'anticipatory' (conditioned) nausea and vomiting, a particularly refractory problem (Morrow, 1982).

1.3 Medical Complications

Indeed there are major medical consequences of severe nausea and vomiting; unusually violent retching may even result in oesophageal tears (Mallory-Weiss syndrome) or in pathological bone fractures. The accompanying dehydration may also exacerbate the nephrotoxicity of certain anticancer drugs. A less dramatic but far more common problem is the prolonged anorexia and malnutrition which compounds the cachexia frequently seen in patients with cancer, making it exceedingly diffi-

cult for the patient to tolerate normal dosages of chemotherapy.

Major metabolic disturbances resulting from vomiting include metabolic alkalosis, chloride and potassium depletion, and extracellular fluid depletion (Dennis, 1982). The degree of the disturbances depends upon the severity and duration of vomiting and the ability of patients to take in fluid during that time, as well as on the compensatory renal mechanism. It is the fluid and electrolyte losses in vomitus which induce metabolic alkalosis and chloride deficiency, but changes in renal function are responsible for maintaining the alkalosis and for developing the potassium deficiency. Thus, extracellular volume depletion is the sum of both gastric and renal losses plus impaired fluid intake. The treatment of fluid and electrolyte disturbances accompanying vomiting is aimed primarily at restoring extracellular volume and chloride. This is most readily accomplished by intravenous saline administration which also prevents further potassium wasting by the kidneys. Depending upon the severity of the previous potassium deficit, it may or may not be necessary to correct the hypokalaemia by oral or intravenous administration of potassium chloride.

2. Considerations in Managing Chemotherapy-induced Emesis

2.1 Contributing Causes

The physician must be familiar with a number of general medical and pharmacological principles when considering the patient who either has suffered from severe nausea and vomiting or is about to receive highly emetic chemotherapy. For example, there are many contributing causes of nausea and vomiting in an individual patient being treated with chemotherapeutic drugs for cancer. It is not usually difficult to exclude some of the more common causes, i.e. intestinal obstruction, peritonitis, or increased intracranial pressure. It is important not to assume that nausea and vomiting are ascribable only to the chemotherapy; excessively prolonged vomiting following a course of chemotherapy should suggest the possibility of alternative medical or psychological causes (Laszlo, 1982).

2.2 Ambulatory or Hospital Management

A related concern in developing a treatment programme is whether the patient can be managed adequately in an outpatient setting or whether the entire treatment should be administered during a brief period of hospitalisation. Factors such as distance from the hospital, the interval between chemotherapy and the onset of the nausea and vomiting, and a supportive home environment, make it preferable for the problem to be dealt with in the outpatient setting. At the same time, some patients may be so incapacitated by retching every 5 to 10 minutes that they need someone to stay with them, and if a suitable person is not available at home, then hospitalisation would be preferable. For patients treated in the clinic, it is important to consider that most antiemetic agents produce sedation when given in the dosage needed to manage nausea and vomiting. Thus patients should be advised to refrain from driving vehicles or working with hazardous machinery while under the influence of some of the drugs.

2.3 Type of Chemotherapy Administered

When considering the drugs which induce nausea and vomiting, we have a general awareness of which are more potent than others (see table I). Clearly, drugs such as cisplatin and cyclophosphamide have a high potential for inducing nausea, vomiting and retching, whereas vincristine and many antimetabolites are far less likely to do so. Dosage is extremely important because the nausea and vomiting produced by low doses of cisplatin may be alleviated by numerous antiemetics,

Table I. Emetic potential of chemotherapeutic drugs[1]

Worst	Moderate	Least
Cisplatin	Nitrosoureas	Vincristine
Dacarbazine	Procarbazine	Vinblastine
Mustine	Mitomycin C	Bleomycin
Doxorubicin		6-Mercaptopurine
Cyclophosphamide		Cytarabine

1 Potency based on usual doses

whereas that produced by high doses of cisplatin responds poorly to almost all antiemetics. No single classification scheme can encompass all these variables together with the fact that some antiemetics are more effective against one agent than another (Neidhart et al., 1981a). The reasons for the latter discrepancies are undoubtedly related to the variable mechanisms of action which emetic chemotherapeutic drugs can exert on the specialised receptor organs in the brain and the gut.

In this symposium, Borison and McCarthy (*page 8*) will review the central neurological inputs and effector mechanisms involved in experimental animals and the concepts on which many clinical studies are based. Among the important conclusions which these workers arrived at is the possibility that nausea, vomiting and retching may be separable, and that combinations of antiemetic agents aimed at the appropriate mechanisms may indeed be rational. Akwari (*page 18*) will review the intestinal physiology of emesis and antiemetic drug action at this locus. This is an exciting area of research which has not yet been fully explored. It seems to have major implications for pharmacological management.

3. *Antiemetic Therapy*

A number of reviews have been written about the pharmacological management of chemotherapy-induced nausea and vomiting (Penta et al., 1981, 1982). Turning first to the standard antiemetic agents, we should begin any such listing with the classic antiemetics – the phenothiazines (see table II). Most of these are very familiar and a good deal has been written about them since they were introduced in the early 1950s. A critical review of the subject is presented in this issue by Wampler (*page 35*). As a class, the phenothiazines are among the most widely used drugs in medical practice, being used mainly in the management of patients with psychiatric disorders. However, phenothiazines are also useful for their antiemetic, antinauseant, and antihistamine properties, as well as for their capacity to potentiate analgesics, sedatives and other central nervous system depressant agents (Lucas, 1982).

Emesis produced by anticancer agents, primarily 5-fluorouracil, has been studied at the Mayo Clinic for many years and drugs such as prochlorperazine and thiopropazate were more effective than placebo in preventing 5-fluorouracil-induced nausea and vomiting (Moertel et al., 1963; Moertel and Reitemeier, 1973). More recent studies have compared various phenothiazines, mainly prochlorperazine, with several newer antiemetics such as tetrahydrocannabinol and nabilone, and in most studies prochlorperazine was less effective than tetrahydrocannabinol or nabilone (Orr et al., 1980; Sallan et al., 1975, 1980). It seems that patients receiving mild emetic stimuli such as 5-fluorouracil or radiation therapy may respond well to phenothiazines whereas those receiving more potent drugs such as cisplatin, and combination chemotherapy with drugs such as doxorubicin and dacarbazine rarely respond satisfactorily (Lucas, 1982). Furthermore, aggressive use of phenothiazines is associated with a considerable number of side effects which are attributable both to the actions of the drugs on the central and autonomic nervous systems and to hypersensitivity reactions.

Antihistamines are often used as antinausea and antiemetic agents. While they work extremely well in motion sickness, they offer little protection

Table II. Antiemetic drugs

Phenothiazines	*Miscellaneous*
Chlorpromazine	Benzquinamide
Prochlorperazine	Haloperidol
Triethylperazine	Droperidol
Promethazine	Metoclopramide
Triflupromazine	Trimethobenzamide
Perphenazine	Diphenidol
	Hyoscine hydrobromide
Antihistamines	Domperidone
Hydroxyzine	
Cyclizine	*Investigational agents*
Meclozine	Tetrahydrocannabinol (THC)
Dimenhydrinate	Nabilone
Buclizine	Levonantradol
Diphenhydramine	Lorazepam
	High dose corticosteroids

against the nausea and vomiting produced by potent chemotherapeutic agents.

A variety of miscellaneous agents have been used in various situations in the management of patients receiving cancer chemotherapy. The more potent of these include benzquinamide derivatives, butyrophenones such as haloperidol and droperidol, the chemically related domperidone, and metoclopramide. For example, Neidhart et al. (1981a) found that benzquinamide completely eliminated vomiting in approximately 20% of patients who received doxorubicin, although it was rarely effective in completely controlling cisplatin- or mustine-induced vomiting, and in addition benzquinamide was occasionally effective even in patients who had been unresponsive to prochlorperazine or haloperidol during prior therapies.

Haloperidol is a major tranquilliser which appears to act as a membrane stabiliser blocking the action of dopamine at the postsynaptic membrane (Janssen, 1967). The drug decreases apomorphine-induced vomiting, suggesting its effectiveness at the chemoreceptor trigger zone (CTZ) as a major mechanism of action. In studies comparing haloperidol with prochlorperazine or tetrahydrocannabinol in patients receiving potent emetogenic chemotherapeutic agents, the overall efficacy of haloperidol was significantly better than benzquinamide and about the same as tetrahydrocannabinol (Neidhart et al., 1981a,b).

Metoclopramide has been highlighted recently by elegant studies at Memorial Sloan-Kettering Cancer Institute in New York. In controlled randomised double-blind studies, the effectiveness of metoclopramide in the management of cisplatin-induced nausea and vomiting has been demonstrated (Gralla et al., 1981). In this symposium (*page 63*), Gralla discusses its development as an antiemetic. This drug has recently been approved by the United States FDA for cisplatin-induced nausea and vomiting and a section of the symposium is devoted to reviewing its pharmacology.

There has been considerable research interest in the use of cannabinoids, which are still experimental drugs, and this field will be reviewed by Vincent and colleagues in this symposium (*page 52*). Δ-9-Tetrahydrocannabinol is the best studied of these and can be either extracted from marijuana plants or synthesised. It is difficult to formulate even in capsule form, but it is an effective antiemetic agent (Laszlo et al., 1981; Neidhart et al., 1981b; Orr et al., 1980; Sallan et al., 1975, 1980). Our studies using tetrahydrocannabinol in 88 patients who had severe nausea and vomiting despite the use of other antiemetics found 18% complete responses, 48% partial responses and 34% less than a partial response. The response rate could be further enhanced with repeated courses of tetrahydrocannabinol. A number of side effects have been reported, with the majority of patients experiencing somnolence and a 'high'. Other side effects include the dysphoric reactions such as fear and anxiety. Interestingly, tetrahydrocannabinol is not particularly helpful in counteracting cisplatin-induced emesis (Laszlo et al., 1981).

Nabilone was the first of the synthetic cannabinoid derivatives described as a significant advance in the management of cisplatin-induced

nausea and vomiting (Herman et al., 1979; Steele et al., 1980). These studies are now amply confirmed.

The effectiveness of the synthetic cannabinoid, levonantradol, after both oral and parenteral administration has been demonstrated in phase I and II studies (Cronin et al., 1981; Laszlo et al., 1981b). It could prove to be an interesting antiemetic agent. Its effectiveness by both the oral and parenteral routes is an important attribute because of the flexibility provided by the parenteral route once the patient begins to vomit. However, at the time of writing, only nabilone and tetrahydrocannabinol seem destined to be marketed for this purpose.

The unresolved question about the cannabinoids is whether their dysphoric properties can be eliminated by pharmacological manipulation of the parent molecule or whether doing so would also eliminate the antiemetic effect.

No review of any pharmacological treatment programme seems complete without mentioning the uses of high dose corticosteroids. A number of provocative articles suggest that high doses of corticosteroids (methylprednisolone, dexamethasone), either alone or in combination with other antiemetics, may be very effective in the treatment of chemotherapy-induced emesis (Rich et al., 1981; Winokur et al., 1981).

Newer chemotherapeutic programmes are more emetic than in the past but, fortunately, major strides in counteracting this problem have also taken place. Physicians recognise that inadequate management of nausea and vomiting is deleterious to the health and well-being of the patient and any delay in providing an aggressive approach aggravates the problem. Once the pattern of nausea and vomiting becomes established, or the patient becomes conditioned during a period of ineffective antiemetic therapy, anticipatory nausea and vomiting become extremely difficult to manage. We hope that this symposium provides some answers which may help the next generation of cancer patients.

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EXHIBIT 7

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE S.A. and ROCHE PALO ALTO LLC.,	
Plaintiffs,	
v.	Civil Action No. 11-3962 (MLC)(DEA) Civil Action No. 11-5579 (MLC)(DEA) (consolidated)
DR. REDDY'S LABORATORIES, LTD., DR. REDDY'S LABORATORIES, INC., SANDOZ INC., TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES, LTD.,	[redacted]
Defendants.	

EXPERT REPORT OF LEE KIRSCH, PH.D.

52. "Only a limited number of chelating agents are used in parenteral products,"[67] and probably the most common chelator that has been used successfully to stabilize intravenous formulations is disodium edetate (*i.e.*, EDTA).[68] For example, Connors 1986 reported:

> The most effective chelating agents used pharmaceutically are ethylenediaminetetraacetic acid (EDTA), citric acid, many of the amino acids, phosphoric acid (weak), and tartaric acid. EDTA and citric acid are two of the most useful agents.[69]

53. In fact, chelating agents like EDTA continue to be the primary excipients of choice for most formulators to this day for drugs that are unstable in liquid formulations, due in part to their prevalent use in prior successful, commercially-approved formulations in the U.S.[70] It would require only quick and routine testing to see whether chelators like EDTA would work to stabilize the oxidative degradation of a compound.

54. Parenteral products, and especially intravenous formulations, must also be made sterile and isotonic in order to reduce the pain that a patient experiences upon injection. Typically, "osmolarities between 280 and 290 mOsm/L are targeted."[71] Common excipients that have been used to adjust the isotonicity of intravenous formulations included sodium chloride,

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[67] Swarbrick 2000 at 140, 142 (Table 3).
[68] *Id.*, *see also* Broadhead 2001 at 341-342; Wells at 172-173, Table 5.6 (EDTA is "particularly effective as a pharmaceutical chelating agent"); Lachman 1986 at 643-644, Tables 22-1 and 22-2, 784; Handbook 2000 at 191-194; DeLuca 1992 at 192-194, Table 5; Dahl 2001 at 169, Table 7.3; Carstensen 2000 at 115; Won 1995 at 103; Turco and King, Sterile Dosage Forms: Their Preparation and Clinical Application, Third Edition, Chpt. 2 at 20-21 (1987) ("Turco 1987"); *see also* 3/15/13 Deposition of Roger Fu at 207:16-23 ("I mean, chelating agent most commonly used is EDTA in the pharmaceutical industry").
[69] Connors 1986 at 100.
[70] Swarbrick 2000 at 140, 142 (Table 3).
[71] Broadhead 2001 at 334; 3/15/13 Deposition of Roger Fu at 82:7-13 (confirming that "it was also common to use a tonicifying agent").

dextrose, and mannitol, and determining the amounts of each to use in order to make a solution isotonic required only routine experimentation.[72]

55. Therefore, within the landscape of what was commonly used at the time of the alleged invention when preparing a stable intravenous formulation for drugs, including palonosetron, even in the absence of more specific prior art teachings, a POSA would have used the routine preformulation studies and have had a reasonable expectation of success at arriving at stable palonosetron formulations – *i.e.*, formulations that were stabilized by optimizing drug concentration and solution pH with a buffer to maintain relatively low pH, and using a chelating agent like EDTA and a tonicifying agent like mannitol.[73] These would be among the few options that would have been tested by a POSA as a matter of course and without undue experimentation, and there is nothing surprising about using this combination of optimized drug concentration, pH, and excipients to formulate palonosetron. Indeed, this system would have been among the systems that a POSA would have tested with a reasonable expectation of successfully stabilizing palonosetron in solution.

3. Strategies for Formulation Screening and Optimization Studies.

56. The particular concentrations of the active drug substance (*i.e.* palonosetron) and inactive excipients that best promoted stability of the formulation also would have been easily determined by a POSA using routine formulation screening and optimization methods or

---

[72] *Id.*; *see also* Lachman 1986 at 642-643, Table 22-1; Handbook 2000 at 324 (disclosing the use of mannitol as a tonicity agent and as "widely used in pharmaceutical formulations"); Physician's Desk Reference, 55th ed., 680-683 (2001); Swarbrick 2000 at 157; *see also* 3/15/13 Deposition of Roger Fu at 103:8-20 (confirming that mannitol was a "quite frequently used" tonicifying agent).

[73] *See also* 5/8/13 Deposition of Kathleen Lee at 234:16-23, 247:16-24 (confirming that preformulation studies were "typically" and "routine[ly]" performed as part of formulation development at Syntex); 3/13/13 Deposition of Andrew Miksztal at 77:3-14 (confirming that preformulation studies were "conducted as a matter of course" and "is a prerequisite activity to formulation development").

Date: September 9, 2013

Lee Kirsch, Ph.D.

EXHIBIT 8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:		)	
		)	
Calderari, et al.		)	Examiner: **Shirley V. Gembeh**
		)	
Serial No.	**11/388,269**	)	Art Unit: **1614**
		)	
Filed:	**March 24, 2006**	)	
		)	
For:	**Liquid Pharmaceutical Formulations of Palonosetron**	)	

AMENDMENT AND RESPONSE TO OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In response to the Office Action mailed in the above-referenced application on July 9, 2008, please enter the following amendments and consider the following remarks.

Amendments to the claims begin on page 2. Claims 1, 8 and 14 are amended. Claim 1 and 3 are canceled. After the amendments, claims 1, 2, 4-10 and 12-24 will remain pending. No new matter is added by the amendments.

Enclosed herewith are the 132 Declaration of Dr. Valentino Stella and a petition for three month extension of time.

Remarks begin on page 5.

REPLACEMENT CLAIMS

1) (CURRENTLY AMENDED) A pharmaceutically stable isotonic intravenous solution for reducing emesis or reducing the likelihood of emesis, formulated by a process that comprises admixing:

   a) ~~a~~ palonosetron or a pharmaceutically acceptable salt thereof in an amount sufficient to yield a concentration of palonosetron or pharmaceutically acceptable salt thereof in the solution of from 0.03 to 0.2 mg/mL;

   b) a chelating agent; and

   c) mannitol in an amount sufficient to render the solution isotonic.

2) (PREVIOUSLY AMENDED) The solution of claim 1 wherein the mannitol is in a concentration of from 40.0 mg/mL to 45.0 mg/mL.

3) (CANCELED)

4) (PREVIOUSLY AMENDED) The solution of claim 1 further comprising admixing a pharmaceutically acceptable acid or base in an amount sufficient to yield a solution having a pH of from 4.0 to 6.0.

5) (PREVIOUSLY AMENDED) The solution of claim 1 wherein said chelating agent comprises from 0.005 mg/mL to 1.0 mg/mL EDTA.

6) (PREVIOUSLY AMENDED) The solution of claim 1 wherein said chelating agent comprises from 10 milliMoles to 100 milliMoles of a citrate buffer.

7) (PREVIOUSLY AMENDED) The solution of claim 1 wherein said palonosetron or pharmaceutically acceptable salt thereof comprises palonosetron hydrochloride.

8) (CURRENTLY AMENDED) A pharmaceutically stable isotonic intravenous solution for reducing emesis or reducing the likelihood of emesis, formulated by a process that comprises admixing:

   a) palonosetron or a pharmaceutically acceptable salt thereof; ~~and~~

   b) a pharmaceutically acceptable carrier in an amount such that said palonosetron or pharmaceutically acceptable salt thereof in said solution is in a concentration of 0.03 mg/mL to 0.2 mg/mL;

c) a chelating agent; and

d) a pharmaceutically acceptable acid or base in an amount sufficient to yield a solution having a pH from 4.0 to 6.0.

9) (ORIGINAL) The solution of claim 8 comprising admixing a pharmaceutically acceptable carrier in an amount such that said palonosetron or pharmaceutically acceptable salt thereof in said solution is in a concentration of about 0.05 mg/mL.

10) (ORIGINAL) The solution of claim 8 wherein the palonosetron or pharmaceutically acceptable salt thereof comprises palonosetron hydrochloride.

11) (CANCELED)

12) (ORIGINAL) The solution of claim 8 wherein the pharmaceutically acceptable carrier comprises from about 0.005 mg/mL to about 1.0 mg/mL EDTA.

13) (ORIGINAL) The solution of claim 8 wherein the pharmaceutically acceptable carrier comprises mannitol.

14) (CURRENTLY AMENDED) A pharmaceutically stable isotonic intravenous solution for reducing emesis or reducing the likelihood of emesis, formulated by a process that comprises admixing:

a) palonosetron hydrochloride ~~or a pharmaceutically acceptable salt thereof~~ in an amount such that said palonosetron in said solution is in a concentration of from 0.03-0.2 mg/mL;

b) a pharmaceutically acceptable carrier; and

c) a pharmaceutically acceptable acid or base in an amount sufficient to yield a solution having a pH from 4.0 to 6.0.

15) (ORIGINAL) The solution of claim 14 comprising a pharmaceutically acceptable acid or base in an amount sufficient to yield a solution having a pH of about 5.0.

16) (ORIGINAL) The solution of claim 14 comprising admixing a pharmaceutically acceptable carrier in an amount such that said palonosetron or pharmaceutically acceptable salt thereof in said solution is in a concentration of about 0.05 mg/mL.

17) (ORIGINAL) The solution of claim 14 wherein the pharmaceutically acceptable carrier comprises a chelating agent.

18) (PREVIOUSLY AMENDED) The solution of claim 14 wherein the pharmaceutically acceptable carrier comprises from 0.005 mg/ml to 1.0 mg/ml EDTA.

19) (ORIGINAL) The solution of claim 14 wherein the pharmaceutically acceptable carrier comprises mannitol.

20) (ORIGINAL) The solution of claim 14 wherein the palonosetron or pharmaceutically acceptable salt thereof comprises palonosetron hydrochloride.

21) (PREVIOUSLY AMENDED) The solution of claim 1 in the form of a solution having a shelf stability of from twelve months to two years when stored at from ten to twenty degrees Celsius.

22) (PREVIOUSLY AMENDED) The solution of claim 8 in the form of a solution having a shelf stability of from twelve months to two years when stored at from ten to twenty degrees Celsius.

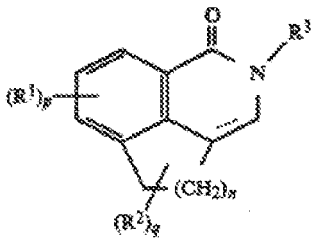
23) (PREVIOUSLY AMENDED) The solution of claim 14 in the form of a solution having a shelf stability of from twelve months to two years when stored at from ten to twenty degrees Celsius.

24) (PREVIOUSLY AMENDED) The solution of claim 16 in the form of a solution having a shelf stability of from twelve months to two years when stored at from ten to twenty degrees Celsius.

BACKGROUND REMARKS

The present invention provides stable isotonic intravenous formulations of palonosetron hydrochloride. The claims do not include oral liquid formulations, which are not isotonic.

The primary prior art cited by the Patent Office is Applicant's original patent for palonosetron, U.S. Patent No. 5,202,333 to Berger et al. The Berger '333 patent describes a class of molecules that share similar structural features with palonosetron, generally described by the following chemical structure designated Formula I in the Berger '333 patent:



I

The Berger '333 patent also describes a wide range of formulation parameters for the compound, including:

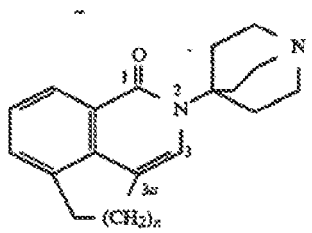
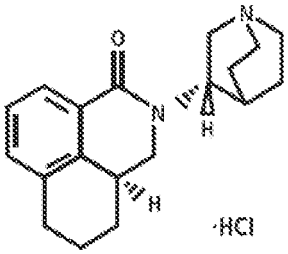
Formulation Parameter	Berger '333 Patent Disclosure
Concentration	"The amount of a compound of Formula I in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, the final composition will comprise from 0.000001% w to 10.0% w of the compound of Formula I, preferably 0.00001% w to 1.0% w, with the remainder being the excipient or excipients." Col. 12, lines 60-68.
Salts	"Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2,-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-

	phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like." Col. 5, lines 1-20.
Formulation types	"Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient." Col. 12, lines 29-35.
Excipients	"Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc.). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols." Col. 12, lines 42-53.
pH	No disclosure of pH by Berger '333 patent; formulation of example 13 in Berger '333 patent gives pH of 3.7 (see background section of current specification).

The Berger '333 patent does not link any particular formulation parameters with any specific compounds, but merely states that a skilled worker can work from these formulation parameters to arrive at a formulation for a particular compound.

Example 13 contains representative oral and intravenous formulations, but not for any particular compounds. Rather, the formulations given in Example 13 are said to be based on the compound of Formula I, which does not include palonosetron hydrochloride because it excludes the salts of Formula I. One notable feature of Example 13 is the recommendation of different product concentrations for oral and intravenous solutions. In particular, Example 13 recommends oral formulations in which the palonosetron concentration ranges from 100-1000 mg / 100 ml, which equates to 0.1-1.0% palonosetron, and intravenous formulations in which the palonosetron concentration ranges from 10-100 mg / 1.0 ml, which equates to 1.0-10% palonosetron.

The Office Action asserts that palonosetron is represented by the formula shown at column 8 of the Berger '333 patent, but that compound binds the isoquinolin and azabicyclo at a different ring position, and has one extra degree of ethylenic unsaturation in the isoquinolin ring:

	
Berger '333 patent, column 8, lines 35-40	Palonosetron hydrochloride

The palonosetron concentration imparts patentability

The current invention lists several critical parameters that must be met for someone to infringe the claim. Most important, the claims require the presence of 0.03-0.2 mg/ml of palonosetron hydrochloride, or a pinpoint concentration of 0.05% in several dependent claims. The Examiner states that this amount is described by the Berger '333 patent but this ignores the fact that the claims are limited to isotonic intravenous solutions, and the only description of isotonic intravenous solutions in the Berger '333 patent is contained in Example 13, in which the range of concentrations for intravenous solutions is given as 1.0-10.0 mg/ml.

The Office argues that the Berger '333 patent describes a composition that comprises "0.000001% w to 10.0% w of the compound of Formula I, preferably 0.00001% w to 1.0% w" at col. 12, lines 60-68, and that the range described in the pending claims is anticipated by this disclosure, but this argument ignores the generality of this disclosure. This broad range covers 5 orders of magnitude of concentrations, is disclosed for any compound within Formula I, and is not limited by formulation type.

The formulation type is an important consideration because Berger recognizes the important relationship between concentration and formulation type. Example 13 recommends oral formulations in which the palonosetron concentration ranges from 100-1000 mg / 100 ml, which equates to 0.1-1.0% palonosetron, but for intravenous formulations the patent recommends palonosetron concentration ranging from 10-100 mg / 1.0 ml, which equates to 1.0-10% palonosetron. Berger's disclosure of different ranges of concentrations based on

formulation indicates that the broad ranges of concentrations that he gives do not apply across the board to every formulation type, but that some consideration must be given to formulation type before selecting an appropriate concentration.

Because the Berger '333 patent describes an extremely broad range of concentrations applicable to all types for formulations, shows through Example 13 that formulation type is important to the concentration of the formulation, and points to a range of concentrations for intravenous formulations in Example 13 that is outside the range of concentrations claimed in the present application, it does not anticipate the narrow range of concentrations claimed in the present application. Compare Atofina v. Great Lakes Chem. Corp., 78 USPQ2d 1417, 1423 (Fed. Cir. 2006) (cited in MPEP section 2131.03) (reference temperature range of 100-500 degrees Celsius did not anticipate range of 330-450 degrees Celsius).

The Berger '333 patent also does not render the concentrations claimed in the present application obvious. As noted above, the patent gives alternative concentration ranges depending on formulation type, and the range given for intravenous formulations does not overlap or include any of the ranges described in the pending claims. The Office has not cited any motivation for deviating from this range of intravenous formulation concentrations, and has not put forth a prima facie case of obviousness.

The Office argues that the concentration in the pending claims would be obvious from the broader ranges described in the patent, but those ranges are extremely broad, ranging from "0.000001% w to 10.0% w of the compound of Formula I, preferably 0.00001% w to 1.0% w." See Berger '333 patent at col. 12, lines 60-68. In addition, the cited ranges are not formulation or compound specific, and Berger recommended concentrations for intravenous formulations of 1.0-10.0 mg/ml. This recommendation teaches away from the current invention and defeats any prima facie case of obviousness. Compare MPEP 2143.02 ("at least some degree of predictability is required"); MPEP 2145 ("References cannot be combined where reference teaches away from their combination.")

A prima facie case of obviousness demands a reasonable expectation of success, In re O'Farrell, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) but, as noted in the enclosed declaration of

Dr. Stella, changing the concentration of the active ingredient can often lead to a more unstable formulation. See Stella Declaration at paragraph 16 ("hydrolytic oxidation is generally more favorable as the concentration of the molecule in water decreases"). To arrive at the claimed formulation, the skilled worker must disregard the preferred concentrations described in Example 13, and select a concentration from the five order of magnitude range of concentrations described in the Berger '333 patent, knowing that any deviations in concentration might impact the stability of the formulation. It is respectfully submitted that a skilled worker would not have a reasonable expectation of success from such experimentation, and that the Berger '333 patent does not support a prima facie case of obviousness.

The Office is expected to contend that this concentration could have been arrived at by routine experimentation and optimization, but this is incorrect because the reference teaches away from the claimed ranges when discussing intravenous formulations. In particular, the reference recommends a concentration range of 1.0-10% when preparing an intravenous formulation, which is well above the range claimed by Applicants. There may be some overlap with the larger concentration ranges described by Berger '333, but those ranges are very broad and they are not formulation specific. Given the unpredictability associated with variations in product concentration (Stella Declaration paragraph 16), and the direction away from the claimed concentration range given by Example 13 of the Berger '333 patent, the claimed concentration could not have been arrived at through routine experimentation and optimization. Compare MPEP 2143.02 ("at least some degree of predictability is required"); MPEP 2145 ("References cannot be combined where reference teaches away from their combination.")

The pH range also imparts patentability

A number of the claims also require that the pH of the formulation be from 4-6, in addition to the limitation on palonosetron concentration. pH is important because, as is well known to pharmaceutical formulators and confirmed by Example 1 of the present application, pH affects the stability of the molecule. The Berger '333 patent does not discuss the impact of

pH on the stability of palonosetron. However, as noted in the background section of the current specification, the intravenous formulation of Example 13 of the Berger '333 patent has an inherent pH of 3.7.

Therefore, in order to arrive at the current invention, a worker of ordinary skill would need to deviate from the Berger '333 patent in two important respects: (1) the worker would need to increase the pH of the formulation above the 3.7 pH inherently described by the Berger '333 patent, and (2) the worker would need to decrease the concentration of palonosetron in the formulation significantly below the 1.0-10.0 mg/ml concentration range described for intravenous formulations in example 13 of the Berger '333 patent. Moreover, the skilled worker would need to make these two movements away from the prior art without knowing how the two variables are inter-related or how each movement would independently impact the stability of the formulation. Given the unpredictability associated with variations in product concentration (Stella Declaration paragraph 16), and the knowledge that pH affects the stability of most drug formulations, a skilled worker would have no expectation of successfully modifying the Berger '333 patent as the Office suggests. In re O'Farrell, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

To overcome this deficiency, the Office cites to a Java applet published on the Internet by Barton et al., but that applet merely "calculates the amount of citric acid and sodium citrate necessary to achieve a buffer at a given pH and strength." See Barton et al. One could plug in a pH of 2.0 and calculate the mass concentrations of citric acid and sodium citrate necessary to achieve it. The office cites to Barton's recommendation "to use citrate buffers only in the pH range 3-6," but Barton says nothing about the optimum pH of a palonosetron formulation, at the concentration described in the pending claims, and whether the palonosetron would remain stable if the pH were raised above the pH of the Berger formulation. Barton does not impart a "reasonable expectation of successfully" increasing the pH from the pH inherently described by Berger, such that a stable formulation results, and does not support a prima facie case of obviousness.

The chelating agent also imparts patentability

The Office Action states that it would have been obvious to incorporate a chelating agent to stabilize the formulation. However, the Office has not cited any prior art that discloses the need for stabilizing a palonosetron formulation, or that a chelating agent would be the right type of compound for accomplishing that stabilization. As stated by Dr. Stella in his declaration:

> 9. Drug substances can undergo chemical degradation by various pathways and mechanisms, including hydrolysis, dehydration, isomerization and racemization, elimination, oxidation, photodegradation, and complex interactions with excipients and other drugs, depending on their chemical structure.
>
> 10. Palonosetron is notable in this respect, because it lacks any of the structural features that commonly favor structural degradation, such as ester groups (which are typically susceptible to nucleophilic attack by water at the ester linkage), amides and imines (as in benzodiazepines, where the ring is susceptible to opening through reversible hydrolysis), carbohydrates (which are frequently lost through acid-catalyzed hydrolysis), or other groups that commonly undergo oxidative degradation (such as ethanolamines to formyl compounds, thiols to disulfides, and sulfur atoms to sulfoxides).
>
> 12. If degradation of palonosetron were suspected, one could not predict from the structure of the molecule how the degradation was occurring. Additional information and teachings would be required.

The inventors have discovered that palonosetron undergoes an auto-oxidation process, but nowhere is such a process described in the prior art cited by the Office. The Office has not cited any prior art showing that that palonosetron is susceptible to degradation, or that such degradation could be overcome by the addition of a chelating agent. In fact, the Applicant has discovered several properties of palonosetron that teach away from the use of a chelating agent. See Stella Declaration at pars. 15-17. In the absence of prior art showing that palonosetron would benefit from the addition of a chelating agent, a skilled worker would not be motivated to include a chelating agent, and a prima facie case of obviousness has not been established.

The use of mannitol also imparts patentability

The Office also contends that it would have been obvious to incorporate mannitol into the formulations of the present invention based on the disclosure of Gambhir, US 5,854,270. This patent discloses oral liquid formulations of ondansetron, and states that the formulation may contain mannitol as a sweetener. However, the current formulation is an isotonic intravenous formulation. It is not an orally administered formulation and does not require sweetening. Gambhir would not have motivated a skilled worker to incorporate mannitol into the claimed intravenous palonosetron formulation, and does not support a prima facie case of obviousness.

CONCLUSION

Based on the foregoing amendments, Applicant respectfully submits that this application is in condition for allowance and earnestly solicits prompt notice of same. Should the Examiner have any questions or concerns regarding this application, she is invited to contact the undersigned at 404-873-8512. To the extent any fees are due for this submission, the Commissioner is authorized to charge deposit account number 012506.

Respectfully submitted,

/s/

Clark G. Sullivan
Reg. No. 36,942

Arnall Golden Gregory LLP
171 17th Street NW
Suite 2100
Atlanta, Georgia 30363
404.873.8512
AGG Docket: 23278.2

EXHIBIT 9

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/186,311	07/21/2005	Giorgio Calderari	06177.105001 (US)	5607

7590 10/06/2008

Clark G. Sullivan
Arnall Golden Gregory LLP
Suite 2100
171 17th Street NW
Atlanta, GA 30363

EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
10/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/186,311	CALDERARI ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/14/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-34,36-44 and 46-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-34,36-44 and 46-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response filed on **7/14/08** presents remarks and arguments to the office action mailed on **10/5/07**. Applicant's request for reconsideration of the rejection of claims in the last office action has been considered.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of Claims

Claims 32-34, 36-44 and 46-50 are pending in this office action. Claims 1-31, 35, 45 and 51-79 are cancelled. Claims 32, 36, 38, 42, 46 and 48 are currently amended.

Declaration 37 C.F.R. §§ 131 of Dr. Daniele Bonadeo.

The Declaration filed on 3/5/08 under 37 CFR 1.131 is sufficient to overcome the 102(e) reference.

Declaration 37 C.F.R. §§ 132 of Dr. Daniele Bonadeo

The Declaration under 37 CFR 1.132 filed on 3/5/08 is insufficient to overcome the rejection of claim 32 and dependant claims based upon the 102(e) and new 103 (a) rejection as set forth in the last Office action because: For the showing of an

unexpected result as relied upon by the Declarant, the showing must truly be unexpected, and a true side by side comparison with the closest prior art and finally, the unexpected result should be commensurate in scope with the claimed invention.

In addressing the declaration, Declarant has shown an unexpected result of a data point within the broadly claimed invention. Claim 32 recites a pharmaceutically stable solution for reducing emesis comprising 0.03-0.2 mg/ml palonosetron, with a pH of 4.0-6.0, in a pharmaceutically acceptable carrier. Interpretation of the above formulation does not have mannitol included in the formulation. Claim 39 of the instant application for example introduces mannitol as one of the many pharmaceutically acceptable carriers capable of forming the formulation with no mention of the concentration. Next, the instant claim 32 is open-ended to various pharmaceutically acceptable carriers capable of forming the formulation, which does not preclude the addition of other ingredients other than those positively recited. Declarant has only addressed one specific formulation within the broader genus which is not commensurate in scope with the current claims and does not overcome the 103 rejection below because the Declaration is very limited, showing a single composition, while the claims are broad and no trend for the unexpected result is shown to hold over the scope of the claim, and again, not a true side by side comparison of the claimed invention.

Example 4 formulation comprises a specific concentration of mannitol (41.5 mg/ml). Thus, Declarant's and Applicant's emphasis on example 4 is very limited and to a very specific palonosetron formulation consisting of specific amount of ingredient

which is narrower limitation of the broad claims. Finally the unexpected result is not unexpected because Gambhir teaches the incorporation of mannitol gave surprising result by virtue of good stability and acceptable taste and further stated that the polyhydric mannitol is added in a range of 20-85% (instant claim 39 and 49). See col.2, lines 32-48 (see below).

Withdrawn Claim Objections

Claim 31 is cancelled therefore the objection is moot.

Withdrawn Claim Rejections - 35 USC § 112

Claims 32-34, 36-44 and 46-50 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn. The claims have been amended.

Withdrawn Claim Rejections - 35 USC § 102

Applicant's Declaration is reviewed with regards to the 102(e) rejection. It is found persuasive in antedating diligence or reduction to practice.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 32-34, 36-44 and 46-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,202,333 in view of Gambhir US 5,854,270 and Applicant's admission and Chaitow, 1990, 3 pages as Evidence by Dickenson US 6,287,592.

Berger et al. teach an oral formulation for reducing emesis comprising palonosetron (100 mg/100ml=0.1mg/ml, a pharmaceutical carrier (dextrose monohydrate) as required by instant claims 32 (in part), 34, 42 (in part) and 44 comprising further, a chelating agent (citric acid, 0.1mg/ml) as required by instant

claims 37 and 47. See col. 27, lines 63-67. Please note that chelating agent is broadly applied, citric acid is known as a chelating agent. The reference also teaches that the formulation may be used orally and intravenously, supra and col. 29, lines 1-12 as required by instant claims 40-41 and 50. The reference teaches that palonosetron is a 5-HT_3 receptor (as defined functionally). The reference further teaches that the concentration of palonosetron will comprise from 0.000001%-10% which is within the claim limitations of instant claims 32-33, 42-43. See col. 12, lines 60-66.

The reference fails to teach the pH of the formulation, the specific chelating agent EDTA and pharmaceutical carrier mannitol for this reason Gambhir is introduced.

Gambhir teaches an anti-emetic liquid formulation comprising ondansetron having a pH range of 2.0-5.0 see abstract and also col. 1 lines 40-41. The reference further teaches that the formulation comprises a polyhydric alcohol, wherein the polyhydric alcohol is mannitol. The reference further teaches that ondansetron is a 5-HT_3 receptor (see col. 1, lines 1-15.

Although, the Berger reference fails to teach the pharmaceutical carrier as mannitol, the Gambhir reference teaches the use of mannitol in a liquid formulation employed for treating emesis. Both references teach the incorporation of a sugar type agent, dextrose and mannitol are both sweeteners. Further as taught by Gambhir, the incorporation of mannitol gave surprising result by virtue of good stability and acceptable taste and further stated that the polyhydric mannitol is added in a range of 20-85% (instant claim 39 and 49). See col.2, lines 32-48.

One of ordinary skill in the art would have been motivated to substitute the dextrose in Berger's formulation for mannitol (Gambhir formulation) in a liquid formulation because as taught in the art it yields good stability and improved taste composition.

With regard to the pH, Gambhir teaches the formulation for emesis has a pH of 2.0-5.0 which falls within the instant claimed limitation (claims 32 and 42 (in part) and 36 and 46. Both references teach that the drugs are 5-HT_3 receptor. Gambhir teaches the pH for a liquid formulation. Together with Applicant's own admission that the pH of the Berger's formulation is 3.7, one of ordinary skill in the art would be motivated to use the teaching of Gambhir (ondansetron-5-HT_3 receptor), and formulate a drug that is a 5-HT_3 receptor to have the same pH because a similar pH has been associated with the 5-HT_3 receptor. Also as taught by Dickenson, the pH of a formulation usually varies depending on the active ingredients and the excipients used. See col. 9, lines 34-36. Therefore, the skilled artisan would be motivated to use the excipients that would maintain the claimed pH of the liquid formulation.

Even though both cited prior arts fail to specifically teach the chelating agent as EDTA, as evidence by Chaitow, EDTA is a more efficient chelating agent see underlining. Therefore, one of ordinary skill in the art would have been motivated to use a more effective chelating agent. The concentration of the chelating agent is 0.1 mg/ml. The determination of a concentration having the optimum therapeutic index is well within the level of the ordinary skill in the art, and the artisan would be motivated to

determine the optimum amounts to get the maximum effect of the drug, hence the reference makes obvious the instant invention.

One of ordinary skill in the art would have been motivated to employ the Bergers stability of 1-2 years as stated in Applicant's specification see page 2 because such stability is expected to be useful with a reasonable expectation of success. It is also taught in the prior art that the addition of one or more polyhydric alcohols (such as mannitol) yielded good stability, therefore with regards to the formulation having improved stability one of ordinary skill in the art would have been motivated to add mannitol as taught by Gambhir and prolong the stability of the formulation.

Thus, the claimed invention was prima facie obvious to make and use.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/S. V. G./
Examiner, Art Unit 1618
9/24/08

EXHIBIT 10

Attorney Docket No. 23278.2
PATENT

CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.

Date: April 6, 2009

/Michelle D. Miller/
Michelle D. Miller

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:		Examiner:	**Shirley V. Gembeh**
Calderari, et al.			
Serial No.	**11/186,311**	Art Unit:	**1614**
Filed:	**July 21, 2005**		
For:	**Liquid Pharmaceutical Formulations of Palonosetron**		

AMENDMENT AND RESPONSE TO OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In response to the Office Action mailed in the above-referenced application on October 6, 2008, please enter the following amendments and consider the following remarks.

Enclosed herewith are the following documents:

- Request is hereby made to extend the time for response to the Office Action of October 6, 2008 to and through April 6, 2009, comprising an extension of the shortened period of Three Months.
- The 132 statutory declaration of Daniele Bonadeo.
- The 132 statutory declaration of Valentino Stella.

Amendments to the claims begin on page 3. No new claims are presented. Claims 1-31, 35, 37, 38, 45, 47 and 51-79 are canceled. Claims 32, 39, 40, 41, and 42 are amended. After the amendments, claims 32-34, 36, 39-44, 46 and 48-50 are pending. Claims 32 and 42 are the only remaining independent claims. No new matter is added by the amendments.

Remarks begin on page 5.

REPLACEMENT CLAIMS

1) – 31) (CANCELED)

32) (CURRENTLY AMENDED) A pharmaceutically stable intravenous solution for reducing emesis or reducing the likelihood of emesis comprising:

a) from 0.03 mg/ml to 0.2 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, buffered at a pH of from 4.0 to 6.0; and

b) a pharmaceutically acceptable sterile aqueous carrier including a tonicifying effective amount of mannitol and from 0.005 mg/ml to 1.0 mg/ml EDTA~~; and~~

~~c) a shelf stability of from twelve months to two years when stored at from ten to twenty degrees Celsius~~.

33) (ORIGINAL) The solution of claim 32 wherein the palonosetron or pharmaceutically acceptable salt thereof is in concentration of about 0.05 mg/ml.

34) (ORIGINAL) The solution of claim 32 comprising palonosetron hydrochloride.

35) (CANCELED)

36) (PREVIOUSLY PRESENTED) The solution of claim 32 wherein the pH is from 4.5 to 5.5.

37)-38)(CANCELED)

39) (CURRENTLY AMENDED) The solution of claim 32 wherein the pharmaceutically acceptable carrier comprises ~~mannitol~~ from 10 to 100 millimoles of a citrate buffer.

40) (CURRENTLY AMENDED) The solution of claim 32 ~~adapted for intravenous administration~~ comprising 0.3 to 0.7 mg/ml EDTA, and from 10 to 40 millimoles of a citrate buffer.

41) (CURRENTLY AMENDED) The solution of claim 32 ~~adapted for oral administration~~ comprising 0.3 to 0.7 mg/ml EDTA, from 10.0 to 80.0 mg/ml mannitol, and from 10 to 40 millimoles of a citrate buffer.

42) (CURRENTLY AMENDED) A pharmaceutically stable isotonic intravenous solution for reducing emesis or reducing the likelihood of emesis comprising:

a) from 0.01 mg/ml to 5 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, at a pH of from 4.0 to 6.0; and

b) an aqueous ~~a~~ pharmaceutically acceptable carrier including a chelating agent; ~~and~~

~~c) a shelf stability of from twelve months to two years when stored at from ten to twenty degrees Celsius~~.

43) (ORIGINAL) The solution of claim 42 wherein the palonosetron or pharmaceutically acceptable salt thereof is in concentration of about 0.05 mg/ml.

44) (ORIGINAL) The solution of claim 42 comprising palonosetron hydrochloride.

45) (CANCELED)

46) (PREVIOUSLY AMENDED) The solution of claim 42 wherein the pH is from 4.5 to 5.5.

47) (CANCELED)

48) (PREVIOUSLY AMENDED) The solution of claim 42 wherein the pharmaceutically acceptable carrier comprises from 0.005 mg/ml to 1.0 mg/ml EDTA.

49) (ORIGINAL) The solution of claim 42 wherein the pharmaceutically acceptable carrier comprises mannitol.

50) (ORIGINAL) The solution of claim 42 adapted for intravenous administration.

51) – 79) (CANCELED)

REMARKS

The present claims are drawn towards pharmaceutically stable intravenous solutions of palonosetron. One of the key aspects of the claims in the requirement for a chelating agent. There is nothing in the prior art that would have motivated a skilled worker to employ a chelating agent such as EDTA in the formulation. In fact, the use of a chelating agent to stabilize this formulation produces unexpected surprising results because Applicant's earlier work with palonosetron suggested that it would not benefit from a chelating agent. As stated in paragraph 16 of the Bonadeo declaration: "The fact that EDTA improves the stability of palonosetron at all is somewhat surprising, given our earliest work with the molecule, in which palonosetron demonstrated comparable stability at 5 °C as it did at 60-100 °C. If the molecule were undergoing auto-oxidation (the typical reason for adding a chelating agent), one would expect the higher temperature to produce more radical initiators and a faster reaction and degradation." This is the exact same conclusion that Dr. Stella reached in paragraphs 15-17 of his declaration that was filed on January 9, 2009. There is nothing about palonosetron that suggests it would have benefitted from a chelating agent, or that would have motivated a skilled worker to use a chelating agent.

The Office Action states that the citric acid in the Berger '333 patent examples is a chelating agent, and that it it would have been obvious to use EDTA instead of the citric acid described in the Berger '333 examples. However, this argument assumes that Berger was using citric acid as a chelating agent when he most likely was using the citric acid to adjust the pH of the solution. As Dr. Stella explains in paragraph 10 of his declaration, the prior art does not teach that a chelating agent should be used with palonosetron because palonosetron "lacks any of the structural features that commonly favor structural degradation."

There is also nothing in the prior art that would have motivated a skilled worker to work with the low concentrations of palonosetron described in the claims. In fact, there are two surprising results associated with this low palonosetron concentration:

(1) The fact that palonosetron becomes more stable as its concentration decreases is surprising, as explained by Dr. Stella in paragraph 16 of his declaration, because

auto-oxidation reactions typically become more favorable as the palonosetron concentration is reduced;

(2) The fact that the chelating agent only works at the lower concentrations of palonosetron described in the claims is also surprising. There is apparently a synergistic relationship between the use of a chelating agent and palonosetron, that only exists at the low concentrations described in the claims. As stated in paragraph 15 of the Bonadeo declaration, "One notable observation from these results is that the presence of EDTA improves stability at low palonosetron concentrations, but actually decreases stability at high palonosetron HCl concentrations." The main prior art cited against this application is the Berger '333 patent, which describes formulations that have higher concentrations of palonosetron. The fact that a chelating agent does not stabilize palonosetron at the higher concentrations taught in the Berger '333 patent, but that it does at the concentrations claimed in this application, further supports the patentability of the present invention.

The Bonadeo declaration also presents evidence of the unexpected stabilizing effect of pH on the formulation. See Bonadeo declaration at par. 10 and Table 2.

TABLE 2. Palonosetron HCl 80 °C pH-Stability Study

pH at Room Temp.	pH at Reaction Temp.	Buffer	T_{90} (days)
2.0	2.0	0.01 M HCl	76
5.0	5.0	Acetate	Not determined. 99.2% remaining at 252 days
7.4	7.3	Phosphate	180
10	9.4	Carbonate	270

Again, this could not have been predicted from the Berger '333 formulation, which had a pH of 3.7. See Bonadeo Dec. at Table 5.

Finally, Claim 41 and 42 are now limited to a very specific formulation, based on the showing in paragraphs 20 and 21 of the attached declaration from Daniele Bonadeo. That declaration presents the following figure 2:

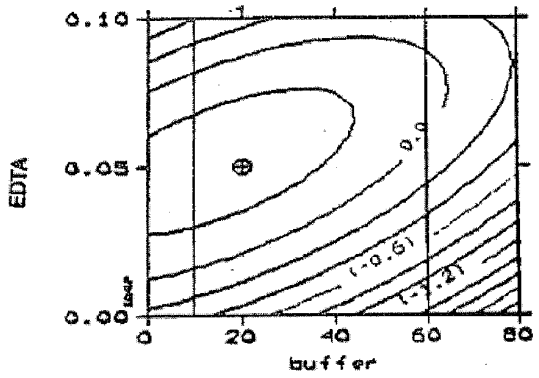


Figure 2

As explained in paragraph 21 of the Bonadeo declaration: "at the low palonosetron concentration depicted, there is a region of no apparent degradation with EDTA from 0.025 to 0.075 % w/v and buffer from 10 to 40 mM. This region is marked by the ⊕ symbol."

The formulation recited in claim 1 is limited to the region marked by a ⊕ symbol in Figure 2, and is almost exactly the same as the formulation shown in this figure, as the following table demonstrates:

Formulation of Claim 1	**Figure 2 Formulation; region denoted by ⊕ symbol**
Citrate buffer 10-40 millimoles	Citrate buffer 10-40 millimoles
EDTA 0.3-0.7 mg/ml	EDTA 0.025-0.075% w/v (i.e. 0.25-0.75 mg/ml)
Mannitol tonicifying agent	Mannitol tonicifying agent
pH 4.0-6.0	pH 5.0
Palonosetron 0.03-0.2 mg/ml	Palonosetron hydrochloride 0.4 mg/ml

Nothing in the prior art would have motivated a skilled worker to employ a citrate buffer and EDTA in the proportions described in claim 1. In fact, these proportions exhibit unexpected surprising results. It could not have been predicted that the combination of EDTA and buffer concentrations in the ⊕ region would produce the most stable formulation, especially in a formulation having a pH of 4-6, mannitol as the tonicifying agent, and a palonosetron concentration of 0.03-0.2 mg/ml

Finally, the Bonadeo declaration includes comparative data in table 5, comparing the predicted stability of the Berger '333 formulation and the claimed formulation in table 5 of the Bonadeo declaration. That table is reproduced below:

TABLE 5

	Berger '333 Example 13 Intravenous Formulation	**Example 4 of Present Application**
Palonosetron Hydrochloride	10-100 mg *	0.05 mg
pH	3.7	5.0
Dextrose monohydrate tonicifying agent	q.s. to render isotonic	--
Mannitol tonicifying agent	--	41.5 mg/ml
Citric acid monohydrate	1.05 mg	1.56 mg
Sodium hydroxide**	0.18 mg	q.s. to pH 5.0 ± 0.5
EDTA	--	0.5 mg
Trisodium citrate	--	3.7 mg
Water for injection	q.s. to 1.0 ml	q.s. to 1.0 ml
1-2 Year Stability?	**NO*** **	**YES**

*Assuming compound of formula I in Example 13 is palonosetron
**Assumes formulation requires pH increase
*** Predicted

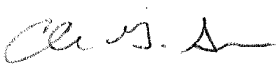
As can be seen, the formulations of the present invention are pharmaceutically stable, when the formulations described in the Berger '333 patent most likely are not. Once again, this data is surprising and unexpected, and supports the patentability of the claimed invention.

CONCLUSION

Based on the foregoing amendments, Applicant respectfully submits that this application is in condition for allowance and earnestly solicits prompt notice of same. Should the Examiner have any questions or concerns regarding this application, he is invited to contact the

undersigned at 404-873-8512. To the extent any fees are due for this submission, the Commissioner is authorized to charge deposit account number 012506.

Respectfully submitted,



Clark G. Sullivan
Reg. No. 36,942

Arnall Golden Gregory LLP
171 17th Street NW
Suite 2100
Atlanta, Georgia 30363
404.873.8512
AGG Docket: 23278.2

EXHIBIT 11

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:		)	
		)	
Calderari, et al.		)	Examiner: **Shirley V. Gembeh**
		)	
Serial No.	**11/388,270**	)	Art Unit: **1614**
		)	
Filed:	**March 24, 2006**	)	
		)	
For:	**Liquid Pharmaceutical Formulations of Palonosetron**	)	

AMENDMENT AFTER FINAL

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In response to the Final Rejection mailed in the above-referenced application on October 29, 2008, please enter the following amendments and consider the following remarks.

A Replacement Claim Set begins on page 2. The claims have been amended to comply with written description objections entered by the Office. No new matter is added by the amendments. After the amendments, claims 1, 2, 5, 8-11, 13, 16-19, 26, 27, 29 and 30 are pending.

REPLACEMENT CLAIM SET

1) (CURRENTLY AMENDED) A pharmaceutically stable intravenous aqueous solution of palonosetron hydrochloride for reducing emesis or reducing the likelihood of emesis comprising

a) from 0.03 mg/mL to 0.2 mg/mL palonosetron and

b) a sterile pharmaceutically acceptable ~~aqueous~~ carrier ~~adapted for intravenous administration,~~ at a pH of from 4.0 to 6.0

and having a shelf stability of from twelve months to two years when stored at from ten to twenty degrees Celsius.

2) (PREVIOUSLY PRESENTED) The solution of claim 1 wherein the palonosetron is in a concentration of about 0.05 mg/mL.

3)-4) (CANCELED)

5) (PREVIOUSLY PRESENTED) The solution of claim 1 wherein the pH is from 4.5 to 5.5.

6)-7) (CANCELED)

8) (ORIGINAL) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises a chelating agent.

9) (PREVIOUSLY PRESENTED) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises from 0.005 mg/ml to 1.0 mg/ml EDTA.

10) (ORIGINAL) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises mannitol.

11) (CURRENTLY AMENDED) A pharmaceutically stable sterile intravenous aqueous solution of palonosetron hydrochloride for reducing emesis or reducing the likelihood of emesis comprising

a) from 0.03 mg/mL to 0.2 mg/mL palonosetron and

b) a pharmaceutically acceptable ~~aqueous~~ carrier.

12) (CANCELED)

13) (CURRENTLY AMENDED) The solution of claim 11 wherein the palonosetron is in a concentration of ~~0.5~~ 0.05 mg/mL.

14)-15)(CANCELED)

16) (PREVIOUSLY PRESENTED) The solution of claim 11 wherein the pH is from 4.5 to 5.5.

17) (PREVIOUSLY PRESENTED) The solution of claim 11 wherein the pharmaceutically acceptable carrier comprises a chelating agent.

18) (PREVIOUSLY PRESENTED) The solution of claim 11 wherein the pharmaceutically acceptable carrier comprises from 0.005 mg/ml to 1.0 mg/ml EDTA.

19) (ORIGINAL) The solution of claim 11 wherein the pharmaceutically acceptable carrier comprises mannitol.

20)-25)(CANCELED)

26) (PREVIOUSLY PRESENTED) The solution of claim 11 in the form of a solution having a shelf stability of from twelve months to two years when stored at from ten to twenty degrees Celsius.

27) (PREVIOUSLY PRESENTED) The solution of claim 13 in the form of a solution having a shelf stability of from twelve months to two years when stored at from ten to twenty degrees Celsius.

28) (CANCELED)

29) (PREVIOUSLY PRESENTED) The solution of claim 16 in the form of a solution having a shelf stability of from twelve months to two years when stored at from ten to twenty degrees Celsius.

30) (PREVIOUSLY PRESENTED) The solution of claim 17 in the form of a solution having a shelf stability of from twelve months to two years when stored at from ten to twenty degrees Celsius.

REMARKS

I. Failure of Prima Facie Case of Obviousness

It is respectfully submitted that the cited references do not support a prima facie case of obviousness.

A. Failure of concentration range

The pending claims describe an intravenous formulation having a palonosetron concentration of 0.03-0.2 mg/ml. The Office asserts that this concentration is described in Example 13 of the Berger '333 patent, which "focuses on a formulation of palonosetron 100 mg/100 ml which equates to 0.1 mg/ml." It is respectfully submitted that the decimal place in the Office Action is misplaced, and that 100mg/100ml actually equates to 1.0 mg/ml, which is outside the 0.03-0.2 mg/ml concentration range in the claims. Example 13 in the Berger '333 patent does not support a prima facie case of obviousness because there is no suggestion or motivation in the example to arrive at the 0.03-0.2 mg/ml claim limitation.

B. Failure of dosage form

It is also notable that the 100mg/100ml formulation from Example 13 of the Berger '333 patent, as cited by the Office, is an oral formulation. In contrast, the pending claims are limited to intravenous formulations. In the absence of some motivation to convert Berger's oral formulation to an intravenous formulation, the reference does not support a prima facie case of obviousness.

Example 13 also describes an intravenous formulation, but this formulation contains 10-100 mg of palonosetron per ml of solution, which equates to a concentration of 10-100 mg/ml. In the absence of some motivation to reduce the concentration of this intravenous formulation

from 10-100 mg/ml to 0.03-0.2 mg/ml, this example also does not support a prima facie case of obviousness.

C. Failure of pH

The Berger '333 patent also fails to teach the 4-6 pH limitation described in the claims. The Office asserts that "there is no independent claim that recites that the pH is necessary for the stability of the pharmaceutically acceptable carrier," but this argument does not address the failure of the reference to teach or suggest a pH of 4-6, as described in the pending claims. In addition, as applicants note in the background on page 2 of the pending application, the intravenous formulation reported by Berger in Example 13 "has a pH of 3.7." In the absence of some suggestion or motivation to increase the pH of Berger's Example 13 formulation from 3.7 to 4.0, the reference does not support a prima facie case of obviousness.

D. Failure of palonosetron hydrochloride

Example 13 of the Berger '333 patent also fails to teach or suggest palonosetron hydrochloride. The Office Action states that Example 13 "clearly focuses on a formulation of palonosetron," but it actually describes a formulation of the "Compound of Formula I," which includes numerous compounds. See column 28, line 57. In the absence of some direction or guidance to select palonosetron from this class of compounds, the examples does not support a prima facie case of obviousness.

II. Improper Use of Result Effective Variable

The Office has previously argued that it would have been obvious to arrive at the claimed concentration of palonosetron, because "the concentration of the drug can be optimized to treat emesis as taught." It is respectfully submitted that the concentration of a

molecule has no bearing on its therapeutic activity. It is the quantity of the molecule administered that determines its therapeutic effect, not its concentration.

What Applicant has discovered, as detailed in Dr. Stella's declaration, is that the stability of palonosetron improves as its concentration decreases. Applicant has discovered that decreasing the concentration of palonosetron improves the stability of the molecule, not that decreasing the concentration improves its therapeutic effect.

The Office could conceivably argue that it would have been routine optimization to lower the concentration to improve the stability of the molecule, but this would be an improper use of a result effective variable. As the MPEP states in section 2144.05(II)(B), "[a] particular parameter must first be recognized as a result-effective variable, i.e. a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation."

As Dr. Stella's declaration makes clear, a skilled worker would not have recognized that lowering the concentration of palonosetron would improve the stability of the molecule, because "hydrolytic oxidation is generally more favorable as the concentration of the molecule in water decreases." In other words, according to Dr. Stella, someone would not optimize the stability of the formulation by lowering the concentration of palonosetron, because it would increase hydrolytic oxidation and decrease molecular stability.

In the absence of any recognition that concentration is a result-effective variable, the Office has not made out a prima facie case for optimizing concentration to arrive at the claimed concentration range.

III. Showing of Unexpected Superior Results

The Office rejects Dr. Stella's declaration because it fails to present side by side experimental results with the closest prior art. However, the experimental results that the Applicant is relying upon are contained in the specification, in Example 2 and the background of the specification. These results are as follows:

	Berger '333 Example 13 Intravenous Formulation*	Example 2 of Present Application**
Palonosetron Concentration	10 mg/ml	0.05 mg/ml
pH	3.7	5.0
1-2 Year Stability?	NO	YES

* As reported in Background of Current Specification; closest formulation
** Optimum Formulation Reported in Example 2

These results show that lowering the concentration of palonosetron from 10 mg/ml to 0.05 mg/ml improves the stability of the molecule. The Office has refused to consider these results but, as stated in MPEP section 716.01(a), "Examiners must consider comparative data in the specification which is intended to illustrate the claimed invention in reaching a conclusion with respect to obviousness of the claims."

The Stella declaration is offered to prove that it would not have been obvious to lower the concentration of Berger's formulation from 10 mg/ml to 0.05 mg/ml, because the stability of compounds such as palonosetron, which are subject to hydrolytic degradation, typically decreases as the concentration of the compound decreases. The Office asserts that it need not accept the Stella declaration because it is "opinion" evidence, but the MPEP makes clear in section 716.01(c)(III) that opinion "testimony is entitled to consideration and some weight so long as the opinion is not on the ultimate legal conclusion at issue." Here Dr. Stella's opinion does not go to the ultimate issue of obviousness, but only whether the results observed by Applicant are unexpected.

When combined with the test results reported in the specification, Dr. Stella's declaration establishes that the invention is supported by unexpected results and that the claims are patentable.

The Office also asserts that the scope of the claims is not commensurate with the showing of unexpected results. According to the Office, "example 2 is to a very specific formulation." But this argument misses the critical point of example 2, which tested

formulations ranging in concentration from 0.05-5.0 mg/ml, and concluded that "greatest stability [is] seen at the lowest palonosetron concentrations." That is precisely what is described in the pending claims, a narrow concentration range of only 0.03-0.2 mg/ml, which is much lower than the 10-100 mg/ml concentration described in the intravenous formulation in example 13 of the Berger '333 patent. Other claims are limited to 0.05 mg/ml, the most stable concentration tested in Example 2. See claims 2 and 13.

In addition, below is a figure taken from this study showing the response surface plot of the degradation rate constant as a function of concentration of palonosetron.

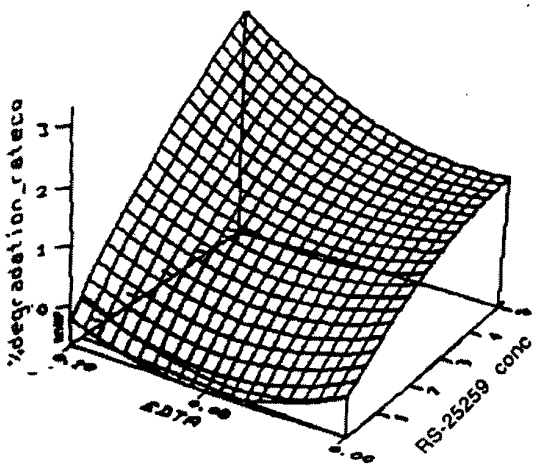


Figure 1

Below is another figure taken from the study, showing a contour plot of potency rate at a palonosetron concentration of 0.4 mg/ml as a function of %EDTA and buffer strength.

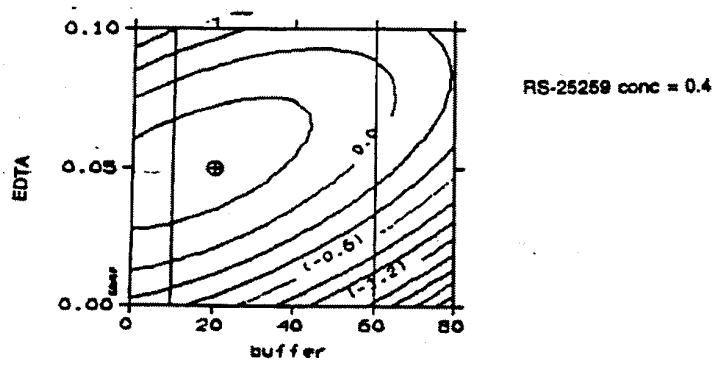


Figure 2

Applicant can present this data by way of declaration if it would prove helpful to the allowance of this application. As can be seen from these figures, the stability of liquid palonosetron formulations is inversely related to the concentration of palonosetron in the formulation, regardless of the concentration of other excipients such as EDTA or buffer. The other excipients may further help stabilize the formulation, but they do not interfere with the effect that palonosetron concentration has on the formulation. This data shows that the concentration of palonosetron is the dominant feature of the present invention, and that the unexpected superior results are commensurate in scope with the claims, which are limited predominantly by concentration and pH.

It is respectfully submitted that Applicant has presented evidence of unexpected superior results, that these results are commensurate in scope with the pending claims, and that the pending claims are non-obvious.

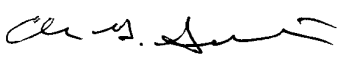
III. 35 USC 112 Rejections

The Office also objects to the claim terminology "acceptable aqueous carrier" and "adapted for intravenous administration," because the terminology allegedly introduces new matter. Applicant respectfully disagrees with the Office, but has amended the claims to use the language suggested by the Office, out of a spirit of cooperation in order to have the application more promptly allowed.

CONCLUSION

Based on the foregoing amendments, Applicant respectfully submits that this application is in condition for allowance and earnestly solicits prompt notice of same. Should the Examiner have any questions or concerns regarding this application, she is invited to contact the undersigned at 404-873-8512. To the extent any fees are due for this submission, the Commissioner is authorized to charge deposit account number 012506.

Respectfully submitted,



Clark G. Sullivan
Reg. No. 36,942

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404.873.8512
AGG Docket: 23278.2

EXHIBIT 12

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/388,270	03/24/2006	Giorgio Calderari	06177.105001 US (CON 1)	7047

7590 10/29/2008

Clark G. Sullivan
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Atlanta, GA 30363

EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
10/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/388,270	CALDERARI ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

The response filed **8/25/08** presents remarks and arguments to the office action mailed **3/25/08**. Applicant's request for reconsideration of the rejection of claims in the last office action has been considered.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of Claims

Claims 1-30 are pending in this office action.

Declaration under 37 C.F.R. §§ 132 of Valentino J. Stella Ph.D.

The Declaration of Valentino J. Stella Ph.D. under 37 CFR 1.132 filed on 8/25/08 is insufficient to overcome the rejection of claim 1 based upon the 103 rejection as set forth in the last Office action because: for the showing of an unexpected result, a true side by side comparison with the closest prior art must be shown, the unexpected result should be commensurate in scope with the claimed invention. Ex parte Gelles 22 USPQ 2d 1318 (at 1319); "The evidence relied upon should be reasonably commensurate in

scope with the subject matter claimed and illustrate the claimed invention “as a class” relative to the prior art.

In addressing the declaration, Declarant stated the following opinions and facts in support of the application: drug substances can undergo chemical degradation by various pathways (item 9), and that palonosetron lacks structural features that commonly favor structural degradation (item 10), that the stability is maintained as the temperature is raised.

After careful review of the Declarant's explanations and opinions, the declaration is found unpersuasive because of the following reasons: there is no showing of a side by side comparison of the closest prior art with the claimed invention. The Declaration filed by Dr. Stella presents opinions and conclusions without supporting facts and as such is entitled to little or no weight. See In re Grunwall 203 USPQ 1055; In re Buchner 18 USPQ 2d 1331 and Ex parte George 21 USPQ 2d 1058. Declarant argues that the Declaration support applicants’ position. The examiner has reviewed the declaration but do not see how it can overcome the 103 rejections. Declarant is of the opinion that the drug substances can undergo chemical degradation by various pathways and mechanisms and that the scientist in Helsinn has observed that the molecule's stability improves in water as its concentration decreases. Declarant further states that this is the opposite of what one normally would expect, because hydrolytic oxidation is generally more favorable as the concentration of the molecule in water decreases. See example 2. There is no comparison of the closest prior art with the claimed example 2. Furthermore, example 2 is to a very specific formulation. Claim one recites 0.03 -0.2

mg of palonosetron and a sterile pharmaceutical acceptable aqueous carrier adapted for intravenous administration at a pH of from 4.0-6.0 with a shelf stability of twelve months to two years. The declaration of Dr. Stella asserts that the stability of the molecule is improved in water as its concentration decreases and further states that the stability is maintained as the “temperature” of the solution is raised to 100 degrees Celsius. This is not commensurate in scope with the claims. The declaration purports the opinion that the prior art combination would not have been completely predictable; however, it is noted that obviousness does not require absolute predictability.

While the affidavit is of an opinion it is not a fact to overcome the 103 rejection. There is no showing of the closest prior art and the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 8-11, 16-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

Claim 1 recites ".... acceptable aqueous carrier... there is no recitation of … acceptable aqueous carrier in the specification. Page 10 of the instant specification recites "typically formulated as aqueous solution". Also, the phrase "adapted for

intravenous administration" is not found in the specification as originally filed. There is formulation for intravenous administration but not adapted as claimed.

Claim Rejections - 35 USC § 103

Claims 1-10 and 21-25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Berger et al. US 5,202,333 (applicant's IDS) in view of Matsumoto, et al., "Yakuzaigaku Manual", Ist edition, Nanzando Co., Ltd. (1989) 2 pages and Barton (Citrate Buffer Calculation, 2000, 2pgs and Castillo et al., US 6,284,749.

Applicant argues that the Berger reference is not focused on any particular dosage forms that the reference teaches wide disclosures of compounds formulations without the necessary directions and guidance from the specification to arrive at the claimed invention. Further Applicant argues that the teaching is not directed to palonosetron or its hydrochloride and fails to meet the claimed concentration of 0.03-0.2 mg/ml. Applicant also argues that the pH of Berger is 3.7 and the stability is less than 1-2 years.

Applicant argues that in the statement of Dr. Stella is exemplified in example 2 of the instant invention and, is superior to example 13 of the Burgers' reference. Also, Applicant asserts that the pH has an independent effect on the stability.

In response, with regard to the Berger's reference not focusing on any particular dosage, this is found not persuasive, because Example 13 clearly focuses on a formulation of palonosetron100 mg/100 ml which equates to 0.1 mg/ml that perfectly embraces the claim limitation recited in the current claim 1. Also, with regard to the pH,

there is no independent claim that recites that the pH is necessary for the stability of the pharmaceutically acceptable carrier and there is no evidence attesting to the significance of the pH. Applicant relies on example 2 in the specification. The example recites palonosetron hydrochloride in the range of 0.05 mg/ml-5.0 mg/ml (again the concentration of Berger is in the claimed range recited), citrate buffer and EDTA, the claims again are not to any specific pharmaceutically acceptable carrier as recited in the instant Example. The term “pharmaceutically acceptable carriers” are open to any pharmaceutically acceptable carrier that could be used in a pharmaceutically suitable solution. Example 2 is very limited, showing a single composition, while the claims are broad and embraces a wide variety of pharmaceutical acceptable carriers in the composition.

As to the argument that is relied upon that the declaration of Dr. Stella asserts that the stability of the molecule is improved in water as its concentration decreases and further states that the stability is maintained as the “temperature” of the solution is raised to 100 degrees Celsius.. This is not commensurate in scope with the claims.

Careful consideration has been given but the argument and the declaration are found not persuasive. The rejection is maintained as set forth in the last office action of record.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/S. V. G./
Examiner, Art Unit 1618
10/10/08

EXHIBIT 13

ATTORNEY DOCKET NO. 23278.2.8401
PATENT

CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.

Date: May 24, 2010

Pamela Mackey
Pamela Mackey

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:		Examiner:	**Shirley V. Gembeh**
Calderari, *et al*			
Serial No.	**11/186,311**	Art Unit:	**1618**
Filed:	**July 21, 2005**		
For:	**Liquid Pharmaceutical Formulations of Palonosetron**		

APPEAL BRIEF

Commissioner for Patents
Mail Stop: Appeal Brief - Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Further to the Notice of Appeal filed in the above-referenced application, Applicant submits this Appeal Brief under 37 C.F.R. § 41.37.

REAL PARTY IN INTEREST

The real party in interest for this appeal is the assignee, Helsinn Healthcare SA, of Lugano Switzerland.

RELATED APPEALS AND INTERFERENCES

There are no related applications under appeal or interference currently pending. An appeal was pending previously in 11/388,270, which is a continuation of the present

application, but that appeal was withdrawn after a conference with the Examiner in which allowable subject matter was agreed upon.

STATUS OF CLAIMS

After an Amendment filed on April 6, 2009, claims 32, 33, 34, 36, 39, 40, 41, 42, 43, 44, 46, 48, 49 and 50 are pending. All claims stand rejected. Claims 1-31, 35, 37, 38, 45, 47 and 51-79 are canceled. No claims are allowed or withdrawn. Appeal is taken of claims 32, 33, 34, 36, 39, 40 and 41.

STATUS OF AMENDMENTS

All amendments to the claims have been entered. The last amendment to the claims was made in an Amendment mailed on April 6, 2010, before the application was finally rejected.

SUMMARY OF CLAIMED SUBJECT MATTER

Claim 32 is the only independent claim on appeal, and it describes an intravenous liquid formulation of palonosetron HCl characterized by a combination of ingredients, ingredient concentrations, and physical characteristics. The claimed formulation is limited by the following features:

(1) an intravenous solution (described in the specification, *inter alia*, at page 8, lines 11-12)

(2) a 0.03-0.2 mg/ml concentration of palonosetron (described in the specification, *inter alia*, at p. 7, lines 1-14) (this and all active ingredient concentrations are based on the weight of palonosetron free base, as described on page 6 at lines 1-3)

(3) a pH of 4-6 (described in the specification, *inter alia*, at p. 7, lines 22-31)

(4) a sterile aqueous carrier (described in the specification, *inter alia*, at page 8, lines 11-12)

(5) mannitol in a tonicifying effective amount (described in the specification, *inter alia*, at page 8, lines 18 and 19)

(6) 0.005-1.0 mg/ml EDTA (described in the specification, *inter alia*, at p. 8, lines 22-24)

Claims 33, 34, 36, 39, 40 and 41 depend from claim 1, and further limit the formulation as follows:

Claim 33: a palonosetron concentration of 0.05 mg/ml (described in the specification, *inter alia*, at p. 8, line 19) (this and all active ingredient concentrations are based on the weight of palonosetron free base, as described on page 6 at lines 1-3)

Claim 34: the hydrochloride salt of palonosetron (described in the specification, *inter alia*, at page 5, lines 16-20)

Claim 36: a pH of 4.5-5.5 (described in the specification, *inter alia*, at p. 7, line 31)

Claim 39: 10-100 millimoles of a citrate buffer (described in the specification, *inter alia*, at p. 8, line 12)

Claim 40: from 0.3 to 0.7 mg/ml EDTA (described in the specification, *inter alia*, at p. 8, line 23); and from 10 to 40 millimoles of a citrate buffer (described in the specification, *inter alia*, at p. 8, line 21)

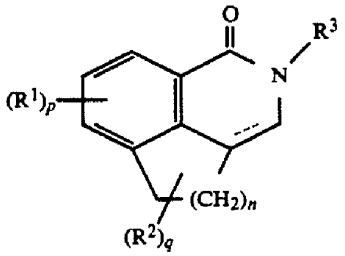
Claim 41: from 0.3 to 0.7 mg/ml EDTA (described in the specification, *inter alia*, at p. 8, line 23); from 10.0 to 80.0 mg/ml mannitol (described in the specification, *inter alia*, at p. p, line 9); and from 10 to 40 millimoles of a citrate buffer (described in the specification, *inter alia*, at p. 8, line 21)

Applicant developed this formulation from scratch, after numerous studies to determine the mechanisms by which palonosetron HCl degrades, and the interaction of various excipients and other formulation parameters on the stability of the molecule. About the only guidance available to the Applicant when it began its development was the structure of palonosetron HCl itself, and that structure gave little clue as to how the molecule should be formulated. As Dr. Stella observes:

> Palonosetron is notable … because it lacks any of the structural features that commonly favor structural degradation … If degradation of palonosetron were suspected, one could not predict from the structure of the molecule how the degradation was occurring. Additional information and teachings would be required. …

Stella Dec. at pars. 10, 12, 22 (Exh. F).

The closest prior art, U.S. Patent No. 5,202,333 to Berger *et al* (the "Berger '333 patent") (Exh. A), describes a genus of compounds of Formula I, which is reproduced below:



I

The description of formulations in the Berger '333 patent relates generally to all compounds of Formula I, and does not specifically apply to palonosetron. See Col. 12, line 1 through column 13, line 7. The reference does not call out palonosetron HCl for any special treatment in terms of formulation or otherwise.

The reference describes an intravenous formulation in Example 13 (columns 28-29), but that formulation also relates generally to Formula I. In addition, it has an active ingredient concentration that is about 200 times greater than the concentration described in the narrowest pending claims (10-100 mg/ml vs. 0.05 mg/ml) and a pH that is lower than the pH recited in the claims (3.7 vs. 4.0-6.0). See Bonadeo Dec. at par. 24 (Exh. E). In addition, the formulation uses dextrose to tonicify the formulation instead of mannitol, and does not include EDTA or any other ingredient for its antioxidant properties.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

This appeal presents only one question for review:

I. Whether claims 32, 33, 34, 36, 39, 40 and 41 fail to comply with 35 U.S.C. § 103 based on the Berger '333 patent (US 5,202,333) in view of Gambhir *et al* (US 5,854,270), Chaitow (1990) and Dickinson *et al* (US 6,287,592).

ARGUMENT

I. Whether claims 32, 33, 34, 36, 39, 40 and 41 fail to comply with 35 U.S.C. § 103 based on the Berger '333 patent (US 5,202,333) in view of Gambhir *et al* (US 5,854,270), Chaitow (1990) and Dickinson *et al* (US 6,287,592).

Citing the Berger '333 patent (Exh. A) in view of Gambhir *et al* (Exh. B), Chaitow (1990) (Exh. C) and Dickinson *et al* (Exh. D), the Office contends that the subject matter of claims 32, 33, 34, 36, 39, 40 and 41 would have been obvious. The Office acknowledges that numerous elements are missing from the primary reference, including the requirements for 0.03-0.2 mg/ml palonosetron, EDTA at specified concentrations, mannitol in a tonicifying effective amount, and a pH of 4.0-6.0, but contends that each one of these features is taught in various prior art references, and that the combination of features described in the claims would have been arrived at in the course of routine optimization.

The Office does not cite any prior art to support its contention that the features described in the claims would have been combined in the course of routine optimization. With respect to the individual elements of the claims, the Office has modified the primary reference as follows:

The 0.03-0.2 mg/ml limitation: According to the Office, the Berger '333 patent generally describes pharmaceutical formulations of palonosetron, and it would have been obvious to use palonosetron at a concentration of 0.03-0.2 mg/ml in a liquid formulation because the Berger '333 patent generally teaches that the formulations may comprise 0.0001%-0.1% palonosetron, which overlaps the 0.03-0.2 mg/ml range described in the claims. It is respectfully noted that the Office's range is not supported by the Berger '333 patent. The preferred concentration range given by Berger '333 patent is actually two orders of magnitude larger, or 0.00001%-1.0% (see col. 12, lines 66-67) which translates to 0.0001-10.0 mg/ml.

The EDTA limitation: The Office contends that it would have been obvious to incorporate EDTA in the formulation because the injection solution described in example 13 of the Berger '333 patent includes citric acid, which is a known chelating agent, and it

would have been obvious to use EDTA instead of citric acid because, according to Chaitow (1990), "EDTA is a more efficient chelating agent."

The mannitol limitation: The Office contends that it would have been obvious to incorporate mannitol into the claimed formulation because the Berger '333 patent teaches that a sugar-type agent such as dextrose can be added to the formulation, mannitol and dextrose are both sweeteners, and Gambhir *et al* teach that mannitol can be used as a sweetener in an oral formulation of ondansetron, which is a 5-HT_3 antagonist like palonosetron.

The pH 4.0-6.0 limitation: The Office contends that it would have been obvious to formulate palonosetron at a pH of 4.0-6.0 because Example 13 of the Berger '333 patent describes an intravenous formulation that has a projected pH of 3.7, Gambhir *et al* teach an oral formulation of ondansetron that has a pH of 2.0-5.0, and Dickinson teaches that the pH of a formulation usually varies depending on the active ingredients and the excipients used.

A. The routine optimization rationale advanced by the Office fails to account for the invention "as a whole."

1. The routine optimization rationale advanced by the Office does not support a *prima facie* case of obviousness.

The Supreme Court has made abundantly clear that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." KSR International Co. v. Teleflex Inc., 550 U.S. 398, 401, 82 USPQ2d 1385, 1395 (2007). Rather, "the question under 35 U.S.C. 103 is … whether the claimed invention as a whole would have been obvious." MPEP 2141.02 (emphasis in original) (citing Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983)). "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." MPEP 2143.01 (emphasis in original) (citing KSR, supra, 550 U.S. at ___, 82 USPQ2d at 1396.)

The claimed formulation is defined by numerous features, including:

(1) an intravenous solution

(2) a 0.03-0.2 mg/ml concentration of palonosetron

(3) a pH of 4-6

(4) a sterile aqueous carrier

(5) mannitol in a tonicifying effective amount

(6) 0.005-1.0 mg/ml EDTA

In its rejection, the Office picks and chooses these features from several references, and then argues in conclusory fashion that it would have been obvious to combine them as a matter of routine optimization. However, "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" KSR, 550 U.S. at ___, 82 USPQ2d at 1396 quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). "A statement that modifications of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references." MPEP 2143.01.IV (citing Ex parte Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (emphasis in original).

The Office advances a "routine optimization" rationale for combining these disparate formulation elements, but routine optimization only occurs "where the general conditions of a claim are disclosed in the prior art." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233 (CCPA 1955). The Aller invention is particularly instructive on this issue. In Aller, the prior art described a chemical reaction performed at a specific temperature (100 °C) in a specific concentration of sulfuric acid (10%); the inventor was trying to claim the identical chemical reaction, performed at 40-80 °C using a sulfuric acid concentration of 25-70%. The Court affirmed a routine optimization finding, but only because the temperature and sulfuric acid concentrations provided a starting point for optimizing for the process, and rendered obvious the identical reaction performed at

40-80 °C using a sulfuric acid concentration of 25-70%. No such starting point is offered in this case.

In this case, the Office has not even identified a formulation that could be optimized. Instead, it starts with a base formulation described in the Berger '333 patent that contains 0.0001-10.0 mg/ml palonosetron. It then modifies the formulation to a palonosetron concentration of 0.03-0.2 mg/ml, adjusts the pH of 4.0-6.0, adds EDTA as a chelating agent, and adds mannitol as a tonicity agent, based on several different references.

Unlike Aller, where "the general conditions of the claim" were contained in a single prior art reference, the general conditions of this claim must be drawn from multiple secondary references and recombined to arrive at the present invention. This is not the type of rejection that "routine optimization" was intended to support – it is a conventional rejection under the teaching / suggestion / motivation ("TSM") test. The Office's approach misapplies the routine obviousness rationale, does not account for the invention as a whole, and does not support a *prima facie* case of obviousness.

2. The record does not support, by a preponderance of the evidence, the routine optimization rationale advanced by the Office.

The rejection also is in error because the preponderance of evidence in this case does not support the routine optimization rationale advanced by the Office. "The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence." MPEP 716.01(d).

In this case, the Office has not cited any prior art to show that all of the features of the claimed formulation would have been combined as a matter of routine optimization. In contrast, Applicant has submitted substantial evidence which proves that the combination of features that defines the claimed formulation is anything but routine. This evidence shows that the claimed formulation was discovered after a sequence of experiments, each building on the prior experiment like a series of building blocks to

arrive at the claimed invention.[1] A different formulation could have been obtained at any step along the way if the experimental sequence had differed. For example, Applicant discovered that mannitol is the best tonicity agent for the formulation, but this discovery was only made after the inventors had settled on an aqueous formulation, using palonosetron HCl at a pH of 4-6. Bonadeo Dec. at par. 26. In like manner, Applicant discovered that EDTA stabilizes the formulation, but it only does so at low concentrations of palonosetron HCl in an aqueous formulation of palonosetron HCl having a pH of 4-6. Bonadeo Dec. at par. 14.

The cited prior art does not come close to supporting a routine optimization finding. The primary reference cited by the Office is the Berger '333 patent, but that reference is directed toward a generic class of compounds defined by Formula I. The reference describes a broad range of potential concentrations of the active compound (0.0001-10 mg/ml) (col. 12, lines 66-67), but these ranges are much broader than the 0.03-0.2 range specified in the pending claims, and they relate to all types of dosage forms and all compounds encompassed by Formula I, not just palonosetron HCl in an intravenous dosage form. The Berger '333 patent also does not describe any mechanisms by which palonosetron HCl might degrade, or the desirability of an antioxidant such as EDTA; it describes numerous liquid excipients other than water, "including ethanol, glycerol, propylene glycol and various oils" (col. 12, lines 47-48); it does not mention mannitol, but instead mentions other tonicity agents such as "saline, dextrose and glycols" (col. 12, line 52); and it does not mention a suitable pH for the formulation or the use of any acids or bases to adjust the pH.

Example 13 describes an intravenous formulation, but this example also relates generally to Formula I. In addition, the concentration of the compound is well above the concentration recited in claim 1 (10-100 mg/ml vs. 0.03-0.2 mg/ml). The formulation lacks an antioxidant such as EDTA, uses a different tonicity agent (dextrose vs.

[1] These studies included: (1) a temperature stability study (Bonadeo Dec. par. 16); (2) a concentration stability study (Bonadeo Dec. par. 8); (3) a pH stability study (Bonadeo Dec. par. 10); (4) a tonicifying agent study (Bonadeo Dec. pars. 12 and 26), and (5) a multi-variate study in which concentrations of palonosetron HCl, buffer, and EDTA concentrations were varied and evaluated for six months (Bonadeo Dec. par. 14).

mannitol), and is outside the pH range described in the claims (3.7 vs. 4-6) (see Bonadeo Dec. at par. 23). The Berger '333 patent fails completely to provide, in its general disclosure or in Example 13, any suggestion of an aqueous isotonic intravenous formulation that comprises palonosetron HCl at a concentration of 0.03-0.2 mg/ml, EDTA, and mannitol at a pH of 4-6, as required by claim 1.

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." KSR, supra, 550 U.S. at 401, 82 USPQ2d at 1395. The record must prove by a preponderance of the evidence that it would have been obvious to combine the elements in the manner claimed. The record in this case does not support the obviousness rejection because it does not support the Office's routine optimization rationale.

3. The record does not support, by a preponderance of the evidence, a reasonable expectation of success for the invention as a whole.

The record also does not support a reasonable expectation of success from combining all of the prior art features into one formulation. Even after KSR, a reasonable expectation of success is demanded for a finding of obviousness. See MPEP 2143.03 (citing KSR, supra, 550 U.S. at 401, 82 USPQ2d at 1395; Sakraida v. AG Pro, Inc., 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); Anderson's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 152, 87 USPQ 303, 306 (1950)). "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." MPEP 2143.01 (emphasis in original) (citing KSR, supra, 550 U.S. at ___, 82 USPQ2d at 1396.)

While the Office has not addressed the issue directly, its "routine optimization" rejection seems to reflect a belief that any drug formulation could and would be developed as a matter of routine experimentation. However, 35 U.S.C. § 103 requires that the formulation would have been obvious from the outset of the development process, not that the formulation would have been obvious in hindsight. See In re Kahn,

441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006) (discussing rationale underlying the motivation-suggestion-teaching test as a guard against using hindsight in an obviousness analysis). While obviousness might be premised on an "obvious to try" rationale, even this rationale requires a "finite number of identified, predictable solutions," a situation that is unsupported by the present record. See KSR, supra, 550 U.S. at 402, 82 USPQ2d at 1396.

The evidence in this case shows that formulation development is highly unpredictable, and that the formulation selected by Applicant is by no means a "predictable solution" to the instability of palonosetron HCl. Numerous factors can and do influence the stability of palonosetron HCl in an aqueous carrier including the concentration of the molecule (Bonadeo Dec. at par. 8); the pH of the solution (Bonadeo Dec. at par. 10); the tonicity agent chosen for the solution (Bonadeo Dec. at par. 26); and the presence of EDTA. (Bonadeo Dec. at par. 14). Viewed "as a whole," these factors reveal much more than a "finite number of solutions yielding predictable results." KSR, supra, 550 U.S. at 402, 82 USPQ2d at 1395. They reveal a non-obvious formulation that is patentable under 35 U.S.C. § 103.

* * * * * *

The problem confronting those of skill in the art here – to develop a stable intravenous formulation of palonosetron from scratch, selecting from numerous formulation variables presented in the prior art -- is analogous to the insurmountable gap found in In re Baird, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994). In In re Baird, a prior art patent provided a broad and general disclosure of a genus of compounds along with description of some more specific subgenera. The patent application at issue in In re Baird was claiming a narrow subgenus of compounds that were encompassed within the large genus of compounds described in the prior art patent. Significantly, however, the prior art patent did not provide any description of species or subgenera that were close in scope to the compounds claimed in the patent application. In reversing an obviousness rejection of the claims in the patent application over the prior art patent, the Federal Circuit held that a broad general disclosure does not make obvious a claim to a species or subgenus that is not described or otherwise specifically suggested by the prior art.

This is analogous to the present rejection as the rejection is applied because the Office has failed to establish why the particular combination of components and features that define the claimed formulation would have been obvious from the myriad of formulation combinations available to the formulation chemist. Nothing in the cited publications specifically describes or suggests an intravenous aqueous solution made up of palonosetron HCl, EDTA, and mannitol at a pH of from 4.0 to 6.0. Following the principle of In re Baird, it would not have been obvious to arrive at the claimed formulation.

B. The record does not support a combination of palonosetron, at a concentration of 0.03-0.2 mg/ml, and EDTA.

As noted above, the Office contends that it would have been obvious to prepare a liquid formulation of palonosetron at a concentration 0.03-0.2 mg/ml, and to incorporate EDTA into that formulation, because the Berger '333 patent states that the compounds of formula I can be formulated at a concentration of 0.001-10.0 mg/ml, and describes an intravenous formulation in Example 13 that contains the compound of Formula I and citric acid, which can act as a chelating agent. According to the Office, it would be obvious to substitute EDTA for citric acid because EDTA is known to be a more effective chelating agent, based on the Chaitow reference.

This rejection is in error because the citric acid described in Example 13 of the Berger '333 patent serves a different function than EDTA. In particular, the citric acid is included as a buffering agent "to maintain the solution at the prescribed pH." Bonadeo Dec. at par. 27. There is no indication that EDTA could serve this purpose, or that the formulation would be operable if the buffering action of citric acid were removed, and EDTA added in its place. It is a basic tenet of the Office's *prima facie* burden that ingredients cannot be substituted in a formulation if they serve a different purpose. "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." MPEP 2143.01.VI (citing In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)

In addition, the Office has not shown a reasonable expectation of successfully combining EDTA with palonosetron HCl. EDTA is added to pharmaceuticals to combat a specific problem – oxidative degradation – and the Office has not cited any prior art suggesting that palonosetron would benefit from the addition of EDTA, or that it would benefit from combating oxidative degradation.

While not stating so expressly, the Office seems to suggest that the formulation chemist would have turned to EDTA as a matter of course if she was experiencing problems with the degradation of the formulation. However, this assumption presupposes an oxidative mode of degradation and, as Dr. Stella testifies, a formulation chemist "could not predict an oxidative pathway for the degradation of palonosetron" based on the structure of palonosetron. Stella Dec. at par. 22. The Office discounts Dr. Stella's testimony as mere "opinion" evidence, but gives no reason for using EDTA instead of the myriad of other stabilization techniques available, cites to no prior art suggesting that palonosetron HCl would benefit from such addition, and offers no basis for reasonably expecting that EDTA would cure any instability of the formulation. Compare Merck & Co., Inc. v. Biocraft Laboratories, Inc., 874 F.2d 804, 809, 10 USPQ2d 1843 (Fed. Cir. 1989) (formulation must be identifiable "by means of routine procedures").

C. The record does not support a combination of palonosetron and mannitol in an isotonic intravenous formulation.

The Office contends that it would have been obvious to incorporate mannitol into the formulation because the Berger '333 patent teaches that a sugar type agent such as dextrose can be added to the formulation, mannitol and dextrose are both sweeteners, and Gambhir *et al* teaches that mannitol can be used as a sweetener in an oral liquid formulation of ondansetron, which is a 5-HT_3 antagonist like palonosetron.

The Office's rejection ignores the fact that the claimed formulations are intravenous formulations, and there would be no reason to include a sweetener from Gambhir's oral formulation in an intravenous formulation. The Office seems to be arguing that the dosage form is a mere statement of use, and that the claimed

formulations include oral liquids, but that argument ignores the requirement of the claims for isotonicity, which in turn is a requirement only for intravenous formulations.

As stated in MPEP 2143.01.I, the prior art must suggest the "desirability" of the claimed invention to support a *prima facie* case of obviousness. Because there is nothing desirable about incorporating a sweetener from an oral liquid into an intravenous formulation, Gambhir *et al* does not support a *prima facie* case of obviousness.

D. The record does not support a formulation at a pH of 4-6.

The Office contends that it would have been obvious to formulate palonosetron at a pH of 4.0-6.0 because Example 13 of the Berger '333 patent describes an intravenous formulation that has a projected pH of 3.7, Gambhir *et al* teaches an oral formulation of ondansetron that has a pH of 2.0-5.0, and Dickinson teaches that the pH of a formulation usually varies depending on the active ingredients and the excipients used.

As the Supreme Court recently stated, "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." KSR, 550 U.S. at ___, 82 USPQ2d at 1396 (quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)). Because Gambhir's teachings address an entirely different molecule than in presently claimed, the reference provides no insight into what pH would be favorable for palonosetron, and does not support a *prima facie* case of obviousness.

Dickinson puts the cart before the horse, and does not cure this deficiency. While it is certainly true that different excipients will result in different pH values, the question for the pharmaceutical formulator is what pH should be used. Until a pH is identified, it would be premature to construct the final formulation.

E. Dependent claims 33, 34, 36, 39, 40 and 41 are narrower and further reinforce the non-obviousness of the claimed invention.

Applicant also notes dependent claims 33, 34, 36, 39, 40 and 41, which further define the formulation based upon a palonosetron concentration of 0.05 mg/ml, the use of

palonosetron hydrochloride, a pH of 4.5-5.5, a citrate buffer and specified concentrations of a citrate buffer, mannitol, and EDTA. The Office has not advanced a *prima facie* rationale for the rejection of these claims, particularly those limited by a citrate buffer. In addition, it is respectfully submitted, these formulations are even further removed from the prior art cited by the Office, which further reinforces the non-obviousness of the present invention. Compare In re Ruschig, 343 F.2d 965, 974, 145 USPQ 274, 282 (CCPA 1965) (Rejection of claimed compound in light of prior art genus inappropriate where the prior art did not disclose a small recognizable class of compounds with common properties.).

F. The claimed formulation exhibits surprising unexpected results.

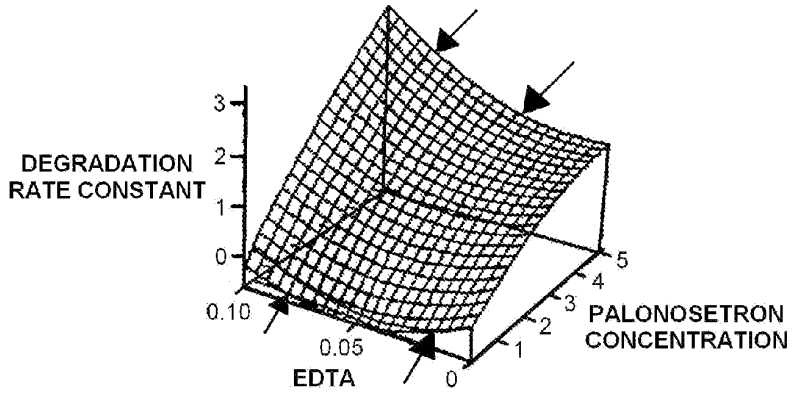
The Office's rejection also fails adequately to account for the unexpected results observed by Applicant. Federal Circuit precedent makes clear that "a greater than unexpected result is an evidentiary factor pertinent to the legal conclusion of obviousness." In re Corkhill, 711 F.2d 1496, 226 USPQ2d 1005 (Fed. Cir. 1995). "Presence of a property not possessed in the prior art is [also] evidence of nonobviousness." MPEP 716.02(a) (citing In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Applicant has made two unexpected discoveries that support the patentability of the present invention.

1. Applicant has discovered an inverse relationship between formulation stability and palonosetron HCl concentration in the presence of EDTA.

Applicant has discovered that EDTA destabilizes palonosetron HCl when added to the high concentration solutions described in the Example 13 Berger '333 patent formulation, but that the opposite occurs in the low concentration solutions described in the claims, where the EDTA actually stabilizes the palonosetron HCl. See Bonadeo Dec. at pars. 14-19 (Exh. E). This discovery is commensurate in scope with the claims because the discovery was made in an aqueous solution buffered at pH 4-6, using mannitol as the tonicity agent, at low concentrations of palonosetron HCl, all as described

in the claims. Compare In re Clemens, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (The "objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support.")

These unexpected results also compare well with the closest prior art (Example 13 of the Berger '333 patent), as illustrated by the following figure adapted from Figure 1 of the Declaration of Daniele Bonadeo:



As can be seen from Figure 1, when the concentration of palonosetron HCl is high, and approaches the concentrations described in Example 13 of the Berger '333 patent (10-100 mg/ml), the addition of EDTA renders the solution less stable, and increases the degradation rate plotted on the z-axis (follow the back line on the EDTA axis from right to left). However, when the concentration of palonosetron HCl is low, and reaches the concentrations described in the pending claims (0.03-0.2 mg/ml), the addition of EDTA renders the solution more stable, and lowers the degradation rate (follow the front line on the EDTA axis from right to left). This comparison to the closest prior art weighs heavily in support of the patentability of the claimed invention. See MPEP 716.02(e) ("An affidavit or declaration under 37 CFR 1.132 must compare the claimed subject matter with the closest prior art to be effective to rebut a *prima facie* case of obvious.")

In effect, Applicant has discovered a "critical" range of concentrations of palonosetron HCl at which EDTA will function. Within these concentrations, EDTA

stabilizes the palonosetron HCl; outside these concentrations EDTA destabilizes palonosetron HCl. "Changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art. ... Such ranges are termed "critical" ranges and the applicant has the burden of proving such criticality." Aller, supra, 220 F.2d at 456, 105 USPQ at 235. This critical range of concentrations, which results in an opposite effect from prior art concentrations and a true "difference in kind," demonstrates the patentability of the presence invention and overcomes the Office's case of obviousness.

The Office discounts this evidence on the ground that the formulation chemist would have observed these results during his efforts at routine optimization. This is improper. The results achieved with a claimed composition cannot be compared to the composition alleged to be obvious because to do so "would be requiring comparison of the results of the invention with the results of the invention." In re Chapman, 357 F.2d 418, 422, 148 USPQ 711, 714 (CCPA 1966). To dismiss applicant's evidence of unexpected results as being present in compositions that would allegedly have resulted from optimization, as the Office does in the rejection, amounts to an improper comparison of the claimed invention to itself.

The Office also errs in alleging that applicant merely recognized an advantage that would flow naturally from following the suggestion of the prior art. While it is true that nonobviousness is not supported by discovery of an inherent property present in prior art compositions, the same is not true of compositions that are not in the prior art. Here, neither the base composition to be optimized nor the specific compositions claimed were in the prior art. Rather, they are merely alleged to have been obtainable through "optimization" of prior art compositions. Thus, the unexpected properties discovered by applicant were not present in any relevant composition in the cited publications and qualify to support an unexpected result. The rationale of the Office on this point again smacks of impermissible comparison of the results of the invention with the results of the invention. Obviousness rejections cannot be bootstrapped in this way.

2. Applicant has discovered that mannitol unexpectedly stabilizes palonosetron HCl in an aqueous intravenous solution.

Applicant has also made an unexpected discovery surrounding the use of mannitol. In particular, Applicant has discovered that mannitol improves the stability of palonosetron HCl in an aqueous intravenous solution. See Bonadeo Dec. at par. 24. In mannitol, the potency of palonosetron HCl was reduced from 96 to 95% (1%), 94 to 93% (1%), and 95 to 94% (1%). In saline under identical conditions the potency of palonosetron HCl was reduced from 98 to 96% (2%), 98 to 94% (4%), and 98 to 96% (2). There is no prior art cited by the Patent Office to suggest this possibility, which again supports the patentability of the claimed invention. See MPEP 716.02(a) ("Presence of a property not possessed in the prior art is evidence of nonobviousness.")

* * * * * *

"The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence." MPEP 716.01(d) (citing In re Oetiker, supra, 977 F.2d 1443, 24 USPQ2d 1443. In this case, there is substantial evidence of non-obviousness, including (1) evidence that Applicant had to develop this formulation from scratch, due to the scarcity of teachings related to palonosetron HCl formulations in the prior art, (2) evidence of the substantial number of variables that had to be manipulated during formulation development to arrive at a stable formulation, (3) evidence of the unpredictable nature of palonosetron HCl stability during formulation development, and (4) evidence of unexpected results that are largely commensurate in scope with the claims and that compare well with the closest prior art. Combined with this evidence is expert testimony attesting to the unpredictability of this art, and the pharmaceutical chemist's inability to predict a stable formulation with any reasonable expectation of success. Weighed against this evidence is prior art that describes (1) very broad formulation parameters for compounds of Formula I, which includes palonosetron HCl (see Berger '333 specification), and (2) a specific intravenous formulation that differs from the claimed formulation in several significant respects (see Berger '333

example 13). When the evidence is properly weighed and evaluated, it is respectfully submitted that it does not support the Office's conclusions of obviousness, and that the rejection should be reversed.

CONCLUSION

For the above and foregoing reasons, Appellant respectfully requests that the Office's grounds of rejection be reversed, and that the application be remanded to the Examiner with instructions to enter a notice of allowance of all pending claims. To the extent any additional fee is owed for this submission, the Commissioner is authorized to charge Deposit Account Number 504667.

Respectfully submitted,

/Clark G. Sullivan/

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APPENDIX 1 – CLAIMS INVOLVED IN APPEAL

32) A pharmaceutically stable intravenous solution for reducing emesis or reducing the likelihood of emesis comprising:

a) from 0.03 mg/ml to 0.2 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, buffered at a pH of from 4.0 to 6.0; and

b) a pharmaceutically acceptable sterile aqueous carrier including a tonicifying effective amount of mannitol and from 0.005 mg/ml to 1.0 mg/ml EDTA.

33) The solution of claim 32 wherein the palonosetron or pharmaceutically acceptable salt thereof is in concentration of about 0.05 mg/ml.

34) The solution of claim 32 comprising palonosetron hydrochloride.

36) The solution of claim 32 wherein the pH is from 4.5 to 5.5.

39) The solution of claim 32 wherein the pharmaceutically acceptable carrier comprises from 10 to 100 millimoles of a citrate buffer.

40) (The solution of claim 32 comprising 0.3 to 0.7 mg/ml EDTA, and from 10 to 40 millimoles of a citrate buffer.

41) The solution of claim 32 comprising 0.3 to 0.7 mg/ml EDTA, from 10.0 to 80.0 mg/ml mannitol, and from 10 to 40 millimoles of a citrate buffer.

APPENDIX 2 – EVIDENCE APPENDIX

Attached hereto are copies of the evidence entered by the Office or relied upon by appellant in the appeal. This evidence was cited by the Office at the noted points during prosecution of this application:

Exhibit A. U.S. Patent No. 5,202,333 to Berger *et al* (relied upon the Office, and made of record by the Office, in an office action mailed October 6, 2008, on page 5)

Exhibit B. U.S. Patent No. 5,854,270 to Gambhir *et al* (relied upon the Office, and made of record by the Office, in an office action mailed October 6, 2008, on page 5)

Exhibit C. Chaitow, 1990, 3 pages, http://www.healthy.net/scr/article.asp?Id=1815 (relied upon the Office, and made of record by the Office, in an office action mailed October 6, 2008, on page 5)

Exhibit D. U.S. Patent No. 6,287,592 to Dickinson (relied upon the Office, and made of record by the Office, in an office action mailed October 6, 2008, on page 5)

Exhibit E. 132 Declaration of Daniele Bonadeo (filed April 6, 2009) (considered and made of record by the Office in an office action mailed May 20, 2009, on pages 2-4)

Exhibit F. 132 Declaration of Valentino Stella (filed April 6, 2009) (considered and made of record by the Office in an office action mailed May 20, 2009)

APPENDIX 3 – RELATED PROCEEDINGS APPENDIX

None

2804498v1

EXHIBIT 14

UNITED STATES PATENT AND TRADEMARK OFFICE

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NOTICE OF ALLOWANCE AND FEE(S) DUE

53449 7590 03/04/2011

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ART UNIT	PAPER NUMBER
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/186,311	07/21/2005	Giorgio Calderari	23278.2.8401	5607

TITLE OF INVENTION: LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$755	$300	$0	$1055	06/06/2011

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

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If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

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B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

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53449 7590 03/04/2011
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/186,311	07/21/2005	Giorgio Calderari	23278.2.8401	5607

TITLE OF INVENTION: LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$755	$300	$0	$1055	06/06/2011

EXAMINER	ART UNIT	CLASS-SUBCLASS
GEMBEH, SHIRLEY V	1628	514-397000

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5. **Change in Entity Status** (from status indicated above)
- ❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- ❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1628	

DATE MAILED: 03/04/2011

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

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